EPA Jacket 11556-128 Vol.2

GREAT LAKES MARKETING RESEARCH

Child Panel

3361 EXECUTIVE PARKWAY, SUITE 201 | TOLEDO, OH 43606 TEL 419.534.4700 | FAX 419.531.8950 ! WWW.GLM.COM

CRP Data Review for Certification

Date:

December 4, 2012

Package:

0.4mL Advantage® II Tube in Foil Pouch 12/12/40 for Small Dog and Small Cat

GLM:

12445 (ID#38993)

Fallure level	Each child was given ten pouches containing tubes. The tubes are not child-resistant. Access to nine was considered a failure. Any opening or leakage was considered a failure.
Child received	At the beginning of each test period, the child received ten pouches. The pouches contained water filled tubes. The tubes were not child-resistant.
Age distribution for children	50 children Age 42-44 months 30% (7 males, 8 females) Age 45-48 months 40% (10 males 10 females) Age 49-51 months 30% (8 males, 7 females)
Access rate	0 children accessed nine pouches in the first five minutes 0 children accessed nine pouches in the second five minutes 0 children accessed in the full ten-minute test period A total of 50 children were tested, First five minutes: 100% Child Effectiveness Full ten minutes: 100% Child Effectiveness
Sites	A total of 13 sites were used to complete the testing of the children. A complete list of site information is detailed in the report. Site 0838: 2 children, Site 1077: 2 children, Site 1275: 2 children, Sile 3460: 4 children, Site 3467: 2 children, Site 3494: 2 children, Site 447 t: 2 children, Site 5509: 2 children, Site 7096: 8 children, Site 7272: 10 children, Site 7310: 4 children, Site 7349: 4 children, Site: 7350: 6 children
Testers	A total of 7 testers were used to complete the panel. Tester 64: 12 children, Tester 75: 12 children, Tester 35: 8 children, Tester 83: 8 children, Tester 74: 6 children, Tester 31: 2 children, Tester 77: 2 children
Findings	This analysis shows that the package described herein meets the requirements of 40 CFR Part 157.
Data collected and verified by:	Great Lakes Marketing 3361 Executive Parkway Toledo, Ohio 43606 Lori Mitchell Dixon, PhD, Project Director

Child-Resistant Packaging (CRP) Child Panel Test of 0.4mL Advantage® II Tube in Foil Pouch 12/12/40 for Small Dog and Small Cat

1. Introduction and Purpose

Bayer Animal Health, Shawnee, Kansas, has been marketing Advantage® II containing 9.1% imidacloprid and 0.46% pyriproxyfen as a spot-on formulation for dogs and cats for the control of fleas (all stages) for several years. This product is sold in four different volumes for dogs and three different volumes for cats. The volumes are based on body weight bands. Canine dosages are 0.4-mL (for dogs up to and including 10 lbs body weight), 1.0mL (for dogs between 11 and 20 lbs), 2.5mL (for dogs between 20 and 55 lbs) and 4.0mL (for dogs greater than 55 lbs). Dose amounts (mL) are filled in individual tubes and each dose size (mL) is currently available in two different package quantities — a 4-tube blister package and a 6-tube blister package. Feline dosages are 0.23mL (for cats and kittens 8 weeks and older and under 5 lbs), 0.4mL (for cats and kittens 8 weeks and older and 5 to 9 lbs) and 0.8mL (for cats 8 weeks and older and 9 lbs and over). As with the canine presentations, the dose amounts (mL) are filled in individual tubes and each dose size (mL) is available in two different package quantities—a 4-tube blister package and a 6-tube blister package.

Instead of marketing the tubes in a blister package, Bayer Animal Health now wants to market the product in a "treasure chest" outer box containing a certain number (4 or 6) of single pouches (a single tube enclosed in a child-resistant pouch). The single pouches are made from aluminum foil (material# 01446067; PET/AL/PE 12/12/40 and/or (material# 80685238 PET/AL/PE 23/12/50) for all sizes (volumes) of the existing tubes based on the results of the child-resistant package (CRP) testing. The selected single pouches will be packaged in one of two sizes of "treasure chest boxes" (4-tubes pack/ box dimension 108 x 34 x 120 mm & 6-tubes pack/ box dimension 108 x 34 x 168 mm).

As the acute toxicity for the Advantage® II formulation in a laboratory animal study with adult rats was below the 1500 mg/kg criteria of 40 CFR Part 157.22(a)(1) and as the product will be recommended for residential use, the product must be packaged in a child-resistant packaging. Based on an earlier CRP testing, the individual tubes alone did not qualify as child-resistant, and therefore were sold in child-resistant blister packages. Thus, the component of the single pouches, the aluminum pouch (and not the enclosed tube), is designed to be child resistant. After discussions with Dr. Rosalind Gross of EPA for the development of the original CRP blister packaging, Bayer Animal Health had agreed to the following criteria for child-resistant packaging testing.

Calculation of the Toxic Dose to a Child

The acute oral LD₅₀ for Advantage® II product (formulation with 9.0% imidacloprid and 0.48%pyriproxyfen) was determined to be 1,098 mg/kg for female rats. ¹

The number of different sized (volume) tubes that would have to be ingested to induce toxicity in a 25 lb (11.4 kg) child is summarized in Table 1. "Toxic dose" for this product as defined in 40 CFR Part 157.22 and that confirmed by Dr. Rosalind Gross of US EPA is the acute oral LD₅₀ value. The density of the product, 1.092 g/mL, was used in the supporting calculations. Therefore, the toxic dose for a 25 lb (11.4 kg) child amounts to 11.5 mL of Advantage® II formulation.

Table 1.
Tube Sizes, Number of Tubes as Toxic Dose for a Child, and Test Failure Criteria

Advantage® II Tube Size (mL)	No. of Tubes* Constitute as Toxic Amount for a Child	Test Failure Criteria (F) (# Tubes Accessed by a Child)
0.23	50 (49.9)	9**
0.4	29 (28.7)	9
0.8	15 (14.4)	9
1.0	12 (11.5)	9
2.5	5 (4.6)	5
4.0	3 (2.9)	3

^{*}Number in the parenthesis is rounded off to the next higher integer. All tubes are single use only, which means each tube contents are used as a single application.

Child-Resistant Package (CRP) Testing of Single Pouches

Bayer's Advantage® II single pouches will be made from two different aluminum (AL) foil types. Each aluminum foil contains a layer of polyethylene terephthalate (PET) on the outside and a layer of polyethylene (PE) on the inside. The specifications for the two foil types are as follows: 1) PET/AL/PE; 12/12/40 microns (material# 01446067) and 2) PET/AL/PE; 23/12/50 microns (material# 80685238).

^{**}Per EPA guidance, accessing a minimum of 9 tubes are recommended as the test failure criteria for child panel testing when 9 tubes represent a toxic dose for a child.

¹ MRID No. 47089411, "An acute oral LD₅₀ study in the rat with M880 Insecticide," EPA Guideline No. 870.1100, Bayer Report No. 75922 (ID No. 23792), D.A. Eigenberg, 2007, 34 pp.

Bayer has conducted CRP testing of single pouches each one containing a 4.0mL, 2.5mL, 1mL, 0.8mL, 0.4mL or 0.23mL tube. The first 4 sizes will continue to be marketed for use in dogs and the last three sizes will continue to be marketed for use in cats. Please note, 0.4mL size is common for both dogs and cats. Therefore, the CRP testing of single pouches made from 12/12/40 aluminum foil type or 23/12/50 aluminum foil type for all sizes of the product would include for each foil type 6 CRP studies (i.e., 6 child panels + 6 senior adult panels) for the dogs and cats. As a guideline requirement for the CRP testing, all plastic tubes were filled with appropriate fill volume of pure water.

The pouch specifications, identification details, and photographs for the pouch tested are presented in Appendix 3

Child-Resistant Packaging (CRP) Child Panel Test of 0.4mL Advantage® II Tube in Foil Pouch 12/12/40

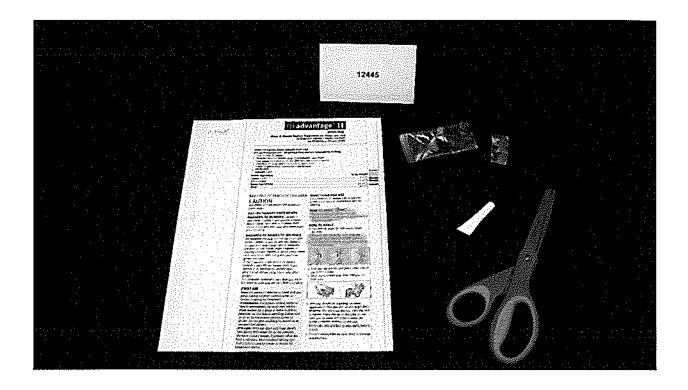
Great Lakes Marketing Research (GLM) conducted a child panel test of 0.4mL Advantage® II Tube in Foil Pouch 12/12/40, Batch No. KP07VF9, using a panel of 50 children aged 42-51 months. The test protocol prescribed in the Federal Register, Title 16, Part 1700.20 was followed.



Ten pouches (12/12/40), each containing a 0.4mL tube, as given to a child for testing (GLM Project No. 12445.



Ten pouches (12/12/40), each containing a 0.4mL tube, as given to a child for testing. One pouch shows its reverse side (GLM Project No. 12445).



Scissors were used for a demonstration by the tester only. A pouch (12/12/40) is photographed showing one end of the pouch cut off with the scissors and the 0.4mL tube is removed from the pouch (GLM Project No. 12445).

Appendix 2 CRP Data Review for Certification (Adult Panel) – ID 38994

GREAT LAKES MARKETING RESEARCH

Senior Panel

3361 EXECUTIVE PARKWAY, SUITE 201 | TOLED**0**, **0**H 43606 TEL 419.S34.4700 | FAX 419.S31.8950 | WWW.GLM.COM

CRP Data Review for Certification

Date:

December 05, 2012

Package:

0.4mL Advantage® II Tube in Pouch Foil 12/12/40 for Small Dog and Small Cat

GLM:

12445 (ID#38994)

Fallure tevel	Failures include those who were unable to open the first pouch and tube, or the second pouch and tube, or unable to open the second pouch and tube in the required 60 seconds.
Adult received	At the beginning of each test period, the adult received one pouch. The adult was allowed up to five-minutes to familiarize themselves with opening the pouch and the tube. The second pouch the adult received required them to open both the pouch and the tube within the one-minute test period.
Age distribution for adults	100 adults Age 50-54 years 25% (8 males, 17 females) Age 55-59 years 25% (7 males, 18 females) Age 60-70 years 50% (15 males, 35 females)
Access rate	0 adults failed to open package A pouch 1 adults failed to open package A tube 0 adults failed to open package B pouch 0 adults failed to open package B tube 1 adult failed to open package B pouch and tube in the required 60 seconds 2 total failures 98.0% Senior Adult Use Effectiveness
Sites	A total of 12 senior adult test sites were used. Site 107: 16 adults, Site 128: 16 adults, Site 246: 13 adults, Site 016: 12 adults, Site 200: 12 adults, Site 004: 9 adults, Site 045: 7 adults, Site 022: 6 adults, Site 094: 4 adults, Site 119: 2 adults, Site 144: 2 adults, Site 003: 1 adult
Testers	A total of 8 testers were used. Tester 71: 24 adults, Tester 76: 22 adults, Tester 88: 17 adults, Tester 85: 16 adults, Tester 30: 14 adults, Tester 38: 4 adults, Tester 61: 2 adults, Tester 40: 1 adult
Findings	This analysis shows that the package described herein meets the requirements of 40 CFR Part 157.
Data collected and verified by:	Great Lakes Marketing Research 3361 Executive Parkway Toledo, Ohio 43606 Lori Mitchell Dixon, PhD, Project Director

Package Description: 0.4mL Advantage® II

Tube in Pouch Foil 12/12/40

Child-Resistant Packaging (CRP) Senior Adult Panel Test of 0.4mL Advantage® II Tube in Pouch Foil 12/12/40

1. Introduction and Purpose

Bayer Animal Health, Shawnee, Kansas, has been marketing Advantage® II containing 9.1% imidacloprid and 0.46% pyriproxyfen as a spot-on formulation for dogs and cats for the control of fleas (all stages) for several years. This product is sold in four different volumes for dogs and three different volumes for cats. The volumes are based on body weight bands. Canine dosages are 0.4-ml. (for dogs up to and including 10 lbs body weight), 1.0-ml. (for dogs between 11 and 20 lbs), 2.5-ml. (for dogs between 20 and 55 lbs) and 4.0-ml. (for dogs greater than 55 lbs). Dose amounts (mL) are filled in individual tubes and each dose size (mL) is currently available in two different package quantities — a 4-tube blister package and a 6-tube blister package. Feline dosages are 0.23-ml. (for cats and kittens 8 weeks and older and under 5 lbs), 0.4-ml. (for cats and kittens 8 weeks and older and 9 lbs and over). As with the canine presentations, the dose amounts (mL) are filled in individual tubes and each dose size (ml.) is available in two different package quantities- a 4-tube blister package and a 6-tube blister package.

Instead of marketing the tubes in a blister package, Bayer Animal Health now wants to market the product in a "treasure chest" outer box containing a certain number (4 or 6) of single pouches (a single tube enclosed in a child-resistant pouch). The single pouches are made from aluminum foil (material# 01446067; PET/AL/PE 12/12/40 and/or (material# 80685238 PET/AL/PE 23/12/50) for all sizes (volumes) of the existing tubes based on the results of the child-resistant package (CRP) testing. The selected single pouches will be packaged in one of two sizes of "treasure chest boxes" (4-tubes pack/ box dimension 108 x 34 x 120 mm & 6-tubes pack/ box dimension 108 x 34 x 168 mm).

As the acute toxicity for the Advantage® II formulation in a laboratory animal study with adult rats was below the 1500 mg/kg criteria of 40 CFR Part 157.22(a)(1) and as the product will be recommended for residential use, the product must be packaged in a child-resistant packaging. Based on an earlier CRP testing, the individual tubes alone did not qualify as child-resistant, and therefore were sold in child-resistant blister packages. Thus, the component of the single pouches, the aluminum pouch (and not the enclosed tube), is designed to be child resistant. After discussions with Dr. Rosalind Gross of EPA for the development of the original CRP blister packaging, Bayer Animal Health had agreed to the following criteria for child-resistant packaging testing.

Calculation of the Toxic Dose to a Child

The acute oral LD₅₀ for Advantage® II product (formulation with 9.0% imidacloprid and 0.48%pyriproxyfen) was determined to be 1,098 mg/kg for female rats.¹

The number of different sized (volume) tubes that would have to be ingested to induce toxicity in a 25 lb (11.4 kg) child is summarized in Table 1. "Toxic dose" for this product as defined in 40 CFR Part 157.22 and that confirmed by Dr. Rosalind Gross of US EPA is the acute oral LD $_{50}$ value. The density of the product, 1.092 g/mL, was used in the supporting calculations. Therefore, the toxic dose for a 25 lb (11.4 kg) child amounts to 11.5 mL of Advantage® II formulation.

Table 1
Tube Sizes, Number of Tubes as Toxic Dose for a Child, and Test Failure Criteria

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^{*}Number in the parenthesis is rounded off to the next higher integer. All tubes are single use only, which means each tube contents are used as a single application.

Child-Resistant Package (CRP) Testing of Single Pouches

Bayer's Advantage® II single pouches will be made from two different aluminum (AL) foil types. Each aluminum foil contains a layer of polyethylene terephthalate (PET) on the outside and a layer of polyethylene (PE) on the inside. The specifications for the two foil types are as follows: 1) PET/AL/PE; 12/12/40 microns (material# 01446067) and 2) PET/AL/PE; 23/12/50 microns (material# 80685238).

^{**}Per EPA guidance, accessing a minimum of 9 tubes are recommended as the test failure criteria for child panel testing when 9 tubes represent a toxic dose for a child.

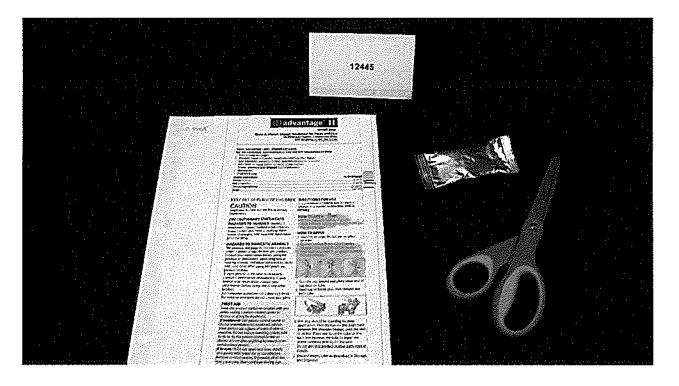
¹ MRID No. 47089411, "An acute oral LD₅₀ study in the rat with M880 Insecticide," EPA Guideline No. 870.1100, Bayer Report No. 75922 (ID No. 23792), D.A. Eigenberg, 2007, 34 pp.

Bayer has conducted CRP testing of single pouches each one containing a 4.0mL, 2.5mL, 1mL, 0.8mL, 0.4mL, or 0.23mL tube. The first 4 sizes will continue to be marketed for use in dogs and the last three sizes will continue to be marketed for use in cats. Please note, 0.4mL size is common for both dogs and cats. Therefore, the CRP testing of single pouches made from 12/12/40 aluminum foil type or 23/12/50 aluminum foil type for all sizes of the product would include for each foil type 6 CRP studies (i.e., 6 child panels + 6 senior adult panels) for the dogs and cats. As a guideline requirement for the CRP testing, all plastic tubes were filled with appropriate fill volume of pure water.

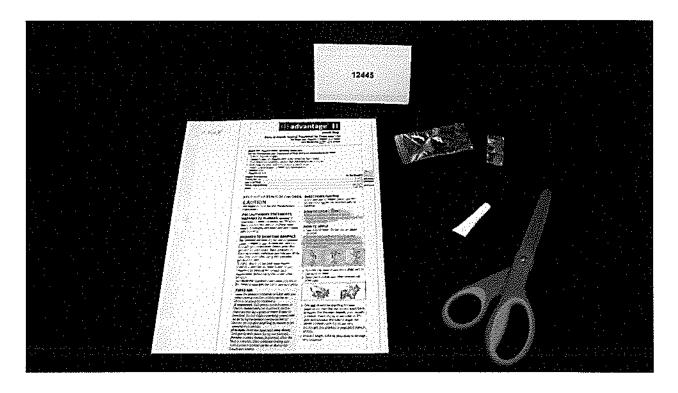
The pouch specifications, identification details, and photographs for the pouch tested are presented in Appendix 3.

Child-Resistant Packaging (CRP) Senior Adult Panel Test of 0.4mL Advantage® II Tube in Pouch Foil 12/12/40

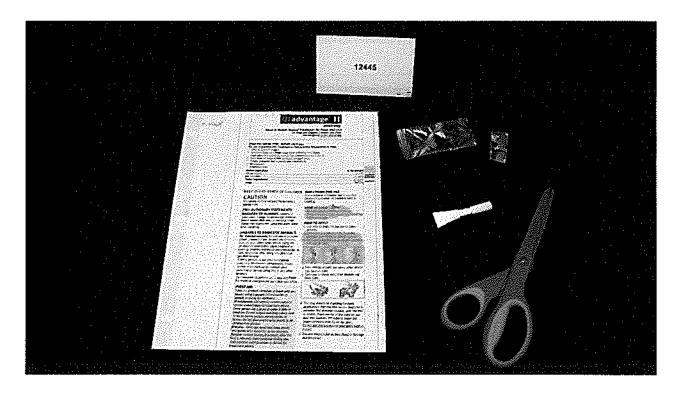
Great Lakes Marketing Research (GLM) conducted a senior adult panel test of 0.4mL Advantage® II Tube in Pouch Foil 12/12/40, Batch No. KP07VF9, using a panel of 100 seniors aged 50-70. The test protocol prescribed in the Federal Register, Title 16, Part 1700.20 was followed.



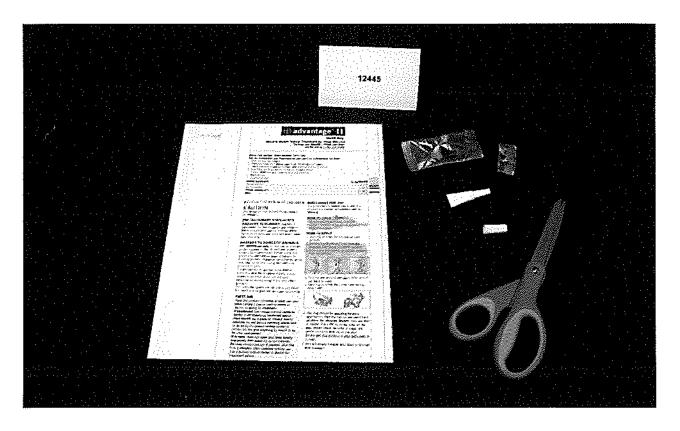
The pouch (12/12/40), opening instructions, and a pair of scissors presented to the senior adults for testing (GLM Project No. 12445).



The pouch (12/12/40) as opened by the senior adult and the 0.4mL tube removed (GLM Project No. 12445).



The 0.4mL tube as opened by the senior adult with the cap reversed to break the seal (GLM Project No. 12445).



The cap removed from the 0.4mL tube by the senior adult to empty the contents in a plastic cup (GLM Project No. 12445).

ATTACHMENT FOR APPLICATION FOR PESTICIDE REGISTRATION December 14, 2012

Advantage II Small Dog (EPA Reg. No. 11556-128)

Purpose of Registration Action: Please find enclosed for the Agency's review and acceptance revised draft labeling, dated 12/12/12, for the subject product. The revisions to this label are only reflective of our enclosed proposal for an additional new childresistant packaging. There have been no revisions of any efficacy claims. Please see the highlighted version of the draft label that shows the changes.

We currently have acceptable CRP packaging (designated as OPTION 1) data on file with the Agency (and the respective CRP Certification letters), but it is our desire to replace the current packaging with a different CRP packaging material (designated as OPTION 2). To do so, we also needed to revise the opening instructions. These new opening instructions were used in the enclosed Child-resistant packaging testing studies.

Packaging: Based on earlier CRP testing, the individual tubes alone did not qualify as child-resistant, and therefore were sold in child-resistant blisters. The current packaging for the products (designated as OPTION 1) has an outer cardboard carton with the tubes in a child-resistant blister. Instead of marketing the tubes in a blister pack, Bayer Animal Health would like the option (designated as OPTION 2) to market the product in a sealed "treasure chest" outer box containing a certain number (4 or 6) of single pouches (a single tube enclosed in a child-resistant pouch). The single pouches are made of aluminum foil [material#01446067; PET/AL/PE 12/12/40] for the existing tubes.

The single-tube pouches will be packaged in one of two sizes of "treasure chest" outer boxes (4-tube pack/box dimension 108 x 34 x 120 mm or 6 tube pack/box dimension 108 x 34 x 120 mm or 6 tube pack/box dimension 108 x 34 168 mm). However, the component of the single pouches, the aluminum pouch (and not the tube or box), is designed to be child resistant.

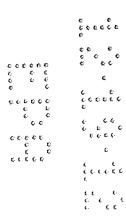
Labeling Changes: The only proposed change to the draft labeling is:

Page 4: Addition of new opening instructions (OPTION 2) - see especially

highlighted draft label.

No other substantive changes have been made to this label, except for those listed above. Therefore, as soon as the data are reviewed and found acceptable, we hope that these changes to the label can be accepted by the Agency for this product, as well as, for the revised labels of the other Advantage II dog products — Advantage II Medium Dog, Advantage II Large Dog, and Advantage II Extra Large Dog - submitted concurrently with this application.

If there are any questions regarding these revisions, please contact us immediately [doug.spilker@bayer.com; (913)-268-2751].





UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

December 27, 2012

OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

BAYER HEALTHCARE LLC

PO.BOX: 390

SHAWNEE MISSION, KS 66201-0390

Report of Analysis for Compliance with PR Notice 11-03

Thank you for your submittal of 19-DEC-12. Our staff has completed a preliminary analysis of the material. The results are provided as follows:

Your submittal was found to be in full compliance with the standards for submission of data contained in PR Notice 11-03. A copy of your bibliography is enclosed, annotated with Master Record ID's (MRIDs) assigned to each document submitted. Please use these numbers in all future references to these documents. Thank you for your cooperation. If you have any questions concerning this data submission, please raise them with the cognizant Product Manager, to whom the data have been released.

PAges 21-32*Claimed confidential by submitter*

21-Day Screen of Amendment (Completed by Contractor)

21-day Expires on 1/9/13

Document Part Of: 1/556-128

MRID, If Any: 440 236

Content Screen: Recommended to Pass/Fail

11-3 Review: Passed/Failed/NA

Overall Status: Pass/Fail

Document returned to:

Steve Schaible

PRIA 2 – 21 Day Content Screen Review Worksheet (EPA/OPP Use Only)

3/23/09

12-19-2012-

Expe	ay Screen Start Date: 12-19-2012 rts In-Processing Signature: 45-45 rts In-management contacted on issues NoY	Date_12-2 esI	6-2012 Date	- Fee I	Paid: Y	es <u>~</u>	
EPA I	Reg. Number: 11566 - 128 EPA Receip	t Date:	12-19	१- २०	12		
	Items for Review				Yes	No	N/A*
1	Application Form (EPA Form 8570-1)(link to form including package type	ı) signed & co	omplete		X		
	Confidential Statement of Formula all boxes compated (EPA Form 8570-4) (Link to form)	pleted, form s	igned, a	nd			X
2	a) All inerts (link to http://www.epa.gov/opprd001) including fragrances, approved for the proposition footnote A) No inerts to review	•	yes	no			
3	Certification with Respect to Citation of Data (Elform) completed and signed (N/A if 100% repack)	A Form 8570	0-34) (L	ink to	X		
	Certificate and data matrix consistent				X		
	If applicant is relying on data that are compensable, to pay statement included. (see Footnote B)	is the offer	yes	no			
4	If applicable, is there a letter of Authorization for exclusive use only. Formulator's Exemption Statement (EPA Form 8570-27) (Link to form) completed and signed (N/A if source is unregistered or applicant owns the technical)			•		X	
	Data Matrix (EPA Form 8570-35) (Link to form) both internal and external copies (PR 98-5) (Link to PR 98-5) completed and signed (N/A if 100% repack)			X			
5	a) Selective Method (Fee category experts use)		yes ×	no			
	b) Cite-All (Fee category experts use)						
	c) Applicant owns all data (Fee category experts u	se)					
6	5 Copies of Label (link to http://www.epa.gov/opi (Electronic labels on CD are encouraged and guidently://www.epa.gov/pesticides/regulating/registering/subrest)	dance is avai	lable)(l	ink to	X		

7	Is the data package consistent with PR Notice 86-5 (link to PRN 86-5)	7	
8	Notice of Filing (link to http://www.epa.gov/pesticides/regulating/tolerance_petitions.htm) included with petitions (link to http://www.epa.gov/pesticides/regulating/tolerances.htm)		X
9	If applicable for conventional applications, reduced risk rationale (link to http://www.epa.gov/opprd001/workplan/reducedrisk.html)		X
10	Required Data (link to http://www.epa.gov/pesticides/regulating/data_requirements.htm) and/or data waivers. See Footnote C. a) List study (or studies) not included with application	-	

Comments:

- · No CSF ho ments to review
- Submitted studies passed PR 11-3 review

 Amendment PASSED

MPID: 490236

* N/A - Not Applicable

Footnotes

A. During the 21 day initial content review, all CSFs will be reviewed to determine whether all inerts listed, including fragrances, are approved for the proposed uses. If an unapproved inert is identified, the applicant must either 1) resolve the inert issue by, for example, removing the inert, substituting it with an approved inert, submitting documentation that EPA approved the inert for the proposed pesticidal uses, correcting mistakes on the CSF, etc. or 2) provide the data to support OPP approval of the inert or 3) withdraw the application. Removing or substituting an inert ingredient will require a new CSF and may require submission of data. All information, forms, data and documentation resolving the inert issue must have been received by the Agency or the application withdrawn within the 21 day period, otherwise, the Agency will reject the application as described below.

To successfully complete this aspect of the 21 day initial content screen, applicants are strongly encouraged to verify that all inert ingredients have been approved for the application's uses even if a product is currently registered by consulting the inert Web site [link to http://www.epa.gov/opprd001/inerts/lists.html] and if the inert is not approved, to obtain the necessary inert approval prior to submitting an application to register a pesticide product containing that inert ingredient. Some inert ingredients are no longer approved for food uses or certain types of uses. The name and/or CAS number on a CSF must match the name and CAS number on this web site. Simple typographical errors in the name or CAS number have resulted in processing delays.

If an inert is not listed on the inert ingredient web site and the applicant believes that the inert has been approved, the applicant should contact the Inert Ingredient Assessment Branch (IIAB) at inertsbranch@epa.gov and resolve the issue. Copies of the correspondence with IIAB resolving the issue should accompany the application. All new inerts except PIP inerts are reviewed by IIAB. The IIAB should also be contacted for any questions on what supporting data needs to be submitted for and the Agency's inert review process. Questions on PIP inerts should be directed to the Chief of Microbial Pesticides Branch [Link to http://www.epa.gov/oppbppd1/biopesticides/contacts_bppd.ltm].

When a brand, trade, or proprietary name of an inert ingredient is listed on a CSF, additional information such as an alternate name of the inert, CAS number or other information [link to http://www.epa.gov/opprd001/inerts/tips.pdf] must also be included to enable the Agency to determine if it has been approved. Each component of an inert mixture (including a fragrance) must be identified. In some cases, the supplier of the mixture or fragrance may need to provide this information to the Agency. Prior to the Agency's receipt of an application, applicants must arrange with a proprietary mixture or fragrance supplier to provide the component information to the Agency or promptly upon EPA's request. If the inert ingredients in a proprietary blend (including fragrances) cannot or are not identified or provided within the 21-day content review period, the Agency will reject the application.

During the 21 day content review, applicants should submit information to the individual identified by the Agency when the applicant is informed of an unapproved inert.

Unapproved Inerts Identified on CSFs

All applications except conventional new products and PIPs

Once an unapproved inert is identified on a CSF, the Agency will contact the applicant with the following options:

- Correct the application by, for instance, correcting the inert's identity or CAS
 number, providing documentation that the inert has been approved, or
 removing the unapproved inert from the CSF or replacing it with one that is
 approved for the application's uses; or
- Submit the information and data needed for the Agency to approve the unapproved inert. If this option is selected and implemented, the Agency may request an extension in the PRIA decision review timeframe to accommodate the inert review/approval process;

3. Withdraw the application (the Agency retains 25% of the full fee for the fee category estimated); or

If none of these options is selected and implemented by the applicant within the 21 day content review period, the Agency will reject the application and retain 25% of the full fee of the category identified.

Conventional New Product Applications

When the Registration Division identifies an unapproved inert on a CSF with an application for a new product that the applicant has not identified as requiring an inert approval (R311, R312 or R313), it will contact the applicant with the following options:

- Correct the application by, for instance, correcting the inert's identity or CAS
 number, providing documentation that the inert has been approved, or
 removing the unapproved inert from the CSF or replacing it with one that is
 approved for the application's uses; or
- 2. Submit the information and data needed for the Agency to approve the unapproved inert, including any required petition to establish or amend a tolerance or exemption from a tolerance. (This option may change the PRIA category for the application, which could require a longer decision review time and a larger fee. If additional fees are due, they must be received by the Agency within the 21 day content review period.)
- 3. Withdraw the application (the Agency retains 25% of the full fee for the fee category estimated); or

If none of the above options is selected and implemented during the 21-day content-review period, the Agency will reject the application and retain 25% of the appropriate fee for the new product-inert approval category.

PIP Applications

When the Biopesticide and Pollution Prevention Division identifies an unapproved inert on a PIP CSF and a request to approve the inert does not accompany the application, it will contact the applicant with the following options:

- Correct the application by, for instance, correcting the spelling or name of the inert to that in 40 CFR 174, or providing documentation that the inert has been approved; or
- 2. Submit the information and data needed for the Agency to approve the unapproved inert. If an inert ingredient tolerance exemption petition is required, the petition must be received by the Agency and the B903 fee paid within the 21 day period. If this option is selected and implemented, the Agency will discuss harmonizing the timeframe for both actions.

3. Withdraw the application (the Agency retains 25% of the full fee for the fee category estimated); or

If none of the above options is selected and implemented during the 21 day content review period, the Agency will reject the application and retain 25% of the fee.

- B. A policy on documentation of offers to pay is still being developed, however, for a me-too or fast track (similar/identical) new product, R300 or A530, an application without the necessary authorizations of offers to pay will be placed into either R301 or A531. The Agency recommends that authorizations of offers to pay be submitted with other PRIA applications to avoid delays in the Agency's decision.
- C. Biopesticide applicants are advised to contact the Agency and discuss study waivers prior to submitting their application to the Agency. Documentation of such discussions should be submitted with the study waiver.



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY WASHINGTON, D.C. 20460

December 21, 2012

OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

OPP Decision Number: D-473348

EPA File Symbol or Registration Number: 11556-128 Product Name: ADVANTAGE II SMALL DOG

EPA Receipt Date: 19-Dec-2012 EPA Company Number: 11556

Company Name: BAYER HEALTHCARE LLC

DOUGLAS A. SPILKER
BAYER HEALTHCARE LLC
ANIMAL HEALTH DIVISION
PO Box 390
SHAWNEE MISSION, KS 66201-0390

SUBJECT: Receipt of Registration Amendment Subject to Registration Service Fee

Dear Registrant:

The Office of Pesticide Programs has received your amendment and certification of payment. If you submitted data with this application, the results of the PRN-2011-3 screen will be communicated separately. During the administrative screen, the Office of Pesticide Programs has determined that this Action is subject to a Pesticide Registration Service Fee as defined in the Pesticide Registration Improvement Act.

The Action has been identified as Action Code: R340

AMENDMENT; NON-FAST TRACK; REVIEW WITHIN RD, E.G. PRECAUTIONARY LABELING;

No additional payment is due at this time.

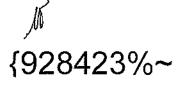
If you have any questions, please contact the Pesticide Registration Service Fee Ombudsman at (703) 308-9362.

Sincerely,

Front End Processing Staff

Information Technology & Resources Management Division

Fee for Service



This package includes the following	for Division
 New Registration Amendment Studies? □ Fee Waiver? □ volpay % Reduction: 	○ AD ○ BPPD ○ RD Risk Mgr. 1
Receipt No. S- EPA File Symbol/Reg. No. Pin-Punch Date:	11556-128 12/20/2012
This item is NOT subject to Action Code: Requested: Re	Parent/Child Decisions:
☐ Inert Cleared for Intended Use Reviewer: Remarks:	☐ Uncleared Inert in Product Date: (2)/2///2

Doug Spilker

From:

paygovadmin@mail.doc.twai.gov

Sent:

Thursday, December 13, 2012 8:55 AM

To:

Doug Spilker

Subject:

Pay.gov Payment Confirmation: PRIA Service Fees

Your payment has been submitted to Pay.gov and the details are below. If you have any questions regarding this payment, please contact Pay.gov Customer Service by phone at (800) 624-1373 or by email at pay.gov.clev@clev.frb.org.

Application Name: PRIA Service Fees Pay.gov Tracking ID: 258TIUSN Agency Tracking ID: 74387651480

Transaction Type: Sale

Transaction Date: Dec 13, 2012 9:54:55 AM

Account Holder Name: Douglas A. Spilker

Transaction Amount: \$3,617.00

Billing Address: 12707 Shawnee Mission Parkway

City: Shawnee State/Province: KS Zip/Postal Code: 66216

Country: USA

Card Type: MasterCard

Card Number: *********0576

Decision Number:

Registration Number: 11556-128

Company Name: Bayer HealthCare, LLC-AH

Company Number: 11556

Action Code: R340

THIS IS AN AUTOMATED MESSAGE. PLEASE DO NOT REPLY.

٠. ٠.

Memorandum

Date:	12 / 28 / 12
To:	7m 01 , Regulatory Manage
From:	Information Services Branch, ITRMD
indicati	ur receipt of this data submission is not an on that MRIDs for the enclosed studies have sted to OPPIN.
from th	e expect that it will be approximately 5 days ne above date before the study-level data is le in OPPIN.
	you have any questions about this process, contact Teresa Downs (305-5363).
This is a	a: fully accepted submission □ partially accepted submission □ rejected submission

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY WASHINGTON, D.C. 20460



OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

JAN 10 2013

Dr. Douglas A. Spilker Bayer Healthcare LLC Animal Health Division P.O. Box 390 Shawnee Mission, KS 66201-0390

Subject:

Notice of Extension of Conditional Registrations until January 17, 2015

Dear Dr. Spilker:

This letter is in reference to your applications dated November 28, 2012, in which you request to extend the following, conditional registrations:

Advantage II Medium Dog	EPA Reg. No. 11556-125
Advantage II Large Dog	EPA Reg. No. 11556-127
Advantage II Small Dog	EPA Reg. No. 11556-128
Advantage II Extra Large Dog	EPA Reg. No. 11556-130
Advantage II Kitten	EPA Reg. No. 11556-150
Advantage II Small Cat	EPA Reg. No. 11556-151
Advantage II Large Cat	EPA Reg. No. 11556-152

The above-referenced registrations contain conditions calling for the registrations to expire two years from the date the products are first released for shipment (i.e., January 17, 2013). Additionally, Bayer is required to adhere to the spot on label mitigation, and to submit quarterly enhanced incident reports and quarterly sales information for each of the above registrations.

The Agency has found Bayer to be in compliance with the terms and conditions for the subject products, and is therefore is granting the request to extend the 2-year time-limited registration restrictions. As such, the following changes are being made to the terms and conditions for the products listed above:

• The 2-year time-limited registration restrictions have been extended for an additional 2 years. The new expiration dates for the registrations listed above are January 17, 2015.

Please note that these products are still subject to all other previously required conditions of registration. If Bayer wishes to remove the time limitations altogether, please submit to the Product Manager an amendment application for each product to change the terms and conditions of the registration. Please include with your submission a written rationale for the removal of the time limitation. As you remember, the Agency included this time limitation as a condition of registration for your products to allow for the post-market surveillance of these products. Therefore, we recommend that you include in your rationale the following information, along with any additional information or analyses you think would be helpful to the agency (e.g., tables, charts, information on stewardship activities, etc...):

- A summary and analysis of the incidents received associated with these products, including information on the following:
 - A comprehensive analysis of incident rates per doses distributed;
 - o An analysis of historical incident trends since the products' release into the marketplace;
 - o An analysis of historical incident trends by weight range of animal, breed, weight range of product, etc...
- If these products are also registered in the European Union or Canada, information on incident rates per doses distributed and trends in those countries.

Please also note that requests to remove the expiration date condition are not subject to PRIA fees and do not have to be submitted under PRIA. However, these would also not be considered 90-day, fast-track submissions in order to allow the EPA enough time to fully evaluate the information provided. After receiving these submissions, the EPA will consider the incidents received since the initial registration; review the information and rationale provided; and make a decision on the request.

If you have any questions, please contact the product manager, Venus Eagle, at eagle.venus@epa.gov or (703) 308-8045.

Regards,

Meredith Laws, Chief

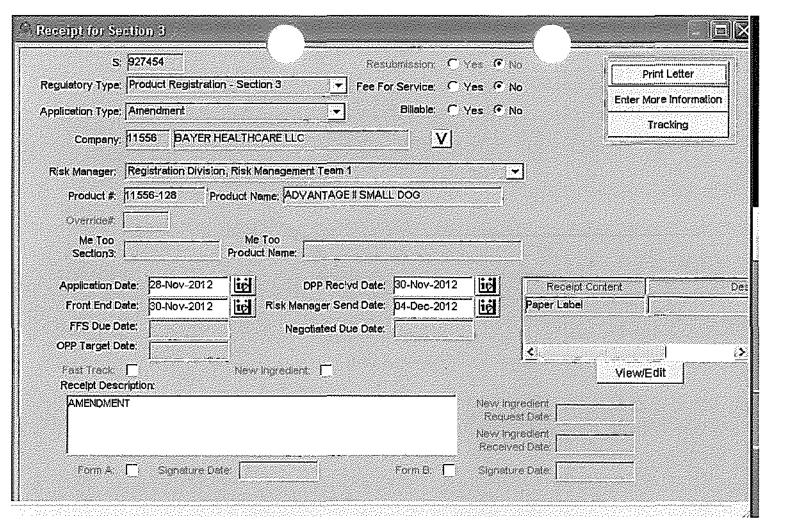
Insecticide-Rodenticide Branch Registration Division (7505P)

Venus Eagle for

¹ http://www.epa.gov/pesticides/health/spot-on-meetings.html

FAST-TRACK AMENDMENTS – Completeness Screening Checklist

E3	xpert's In-Processing Signature: Date: 2/6/12	PM #: _		-
EPA R	Leg. Number: $1 SS_0-128 = 125$ EPA Receipt Date: $1 -3 $:0-13	2	
	Checklist Item	Yes	No	N/A
1	Application Form (EPA Form 8570-1) - signed?	V		
2	Confidential Statement of Formula (EPA Form 8570-29) - signed?			
3	Certification with Respect to Citation of Data (EPA Form 8570-34) - signed?			
4	Formulator's Exemption Statement (EPA Form 8570-27) - signed?			
5	Data Matrix (EPA Form 8570-35) [Applicable for adding me-too uses] - signed? a) Selective Method? b) Cite-All Method?			
	c) Public copy of Matrix provided? See PR Notice 98-5			
6	ls Label included? (5 copies)			
	a) Electronic Label submitted?			
•	Comments: Service Comments:			





NITÈ ATES ENVIRONMENTAL PROTECTIÒ WASHINGTON, D.C. 20460

∌ENCY

December 4, 2012

OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

DR. BRUCE MARTIN
BAYER HEALTHCARE LLC
ANIMAL HEALTH DIVISION
PO Box 390
SHAWNEE MISSION, KS 66201-0390

PRODUCT NAME: ADVANTAGE II SMALL DOG COMPANY NAME: BAYER HEALTHCARE LLC

OPP IDENTIFICATION NUMBER: EPA FILE SYMBOL: 11556-128 EPA RECEIPT DATE: 11/30/12

SUBJECT: RECEIPT OF AMENDMENT

DEAR REGISTRANT:

The Office of Pesticide Programs has received your application for an amendment and it has passed an administrative screen for completeness.

During the initial screen we determined that the application appears to qualify for fast track review. The package will now be forwarded to the Product Manager for review to determine its acceptability for fast track status.

If you have any questions, please contact Registration Division, Risk Management Team 1, at (703) 308-8045.

Sincerely,

Front End Processing Staff Information Services Branch

Information Technology & Resources Management Division

Fee for Service

{9274547~

This package includes the following	for Division
New Registration● Amendment	○ AD ○ BPPD ○ RD
□ Studies? □ Fee Waiver? □ volpay % Reduction:	Risk Mgr. 1
Receipt No. S- EPA File Symbol/Reg. No. Pin-Punch Date:	927454 11556-128 11/30/2012
This item is NOT subject t	to FFS action.
Action Code: Requested: Granted: Amount Due: \$	Parent/Child Decisions:
Inert Cleared for Intended Use Reviewer:	☐ Uncleared Inert in Product Date: \(\frac{12-4-4}{2}\)
Remarks:	

Bayer HealthCare Animal Health



Via Federal Express

November 28, 2012

Document Processing Desk (Non-PRIA Action) Office of Pesticide Programs (7505P) U.S. Environmental Protection Agency Room S-4900, One Potomac Yard 2777 South Crystal Drive Arlington, VA 22202-4501

Attention: Ms. Venus Eagle/PM 01

Request for Extension of Time-limited Registrations for the Subject:

following products:

Advantage II Medium Dog (EPA Reg. No. 11556-125) Advantage II Large Dog (EPA Reg. No. 11556-127) Advantage II Small Dog (EPA Reg. No. 11556-128) Advantage II Extra Large Dog (EPA Reg. No. 11556-130)

Dear Ms. Eagle:

Reference is made to the current registrations of the subject products, and the Agency's letter to us, dated September 20, 2011 (received October 11, 2011), regarding "Implementation of Label Changes to Pet Spot-on Products." In that letter, certain actions were required by us, the registrant, to maintain these registrations. These registrations were designated as "Time-limited" with an expiration date of January 17, 2013. Since we have complied with the conditions of the aforementioned Agency letter, we request an extension of these registrations, until such time as to allow us to pursue the complete removal of the time limitations.

On November 7, 2012, the Agency accepted draft labeling, dated 09/25/2012, for each of the subject dog spot-on products with the revisions outlined aforementioned appropriate in the "Implementation" letter, and subsequent requests of the Agency. Also as required, we submitted the respective printer's proofs of each of the elements of the Final Printed Labeling (packaging) for these products.

Bayer HealthCare LLC Animal Health P.O. Box 390 Shawnee Mission, KS 66201-0390 Furthermore, we have submitted the required quarterly enhanced incident reports for these products beginning with the products' initial releases for shipment (6 quarters). Adverse incident reports have been and continue to be monitored in accordance to the stipulations of the conditional registration. Analysis of the accumulated incident reporting for the initial eighteen (18) months of commercial distribution of the Advantage II Dog registrations indicate occurrence rates to remain very rare. Actual rates (expressed as the ratio incident: doses sold) were 1:12,791, 1:15,601, 1:15,566 and 1:12,277 for the Small Dog, Medium Dog, Large Dog and Extra Large Dog respectively.

Since we have complied with the conditions of the aforementioned Agency's letter to us, dated September 20, 2011, we request an extension of these registrations as soon as possible, since these registrations have an expiration date of January 17, 2013. Enclosed are additional draft copies of the EPA stamped-accepted labels for these products (only the internal version code and date of draft has changed) for your use in processing this request.

In a separate submission, we will be provide an analysis of the submitted enhanced incident reports of these products showing that there is no longer a need for these products to have time-limited registrations based on the safe use history of these products on the respective companion animals.

If you have any questions, please do not hesitate to call (913-268-2751).

Sincerely

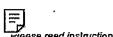
Douglas A. Spilker. Ph. D.

Manager, EPA Regulatory Affairs

Doug.Spilker@Bayer.com

Enclosures:

- 1) Advanatge 11 Small Dog Application
- 2) Advantage II Small Dog Draft label, dated 11/28/12 (1 copy)
- 3) Advanatge Il Medium Dog Application
- 4) Advantage II Medium Dog Draft label, dated 11/28/12 (1 copy)
- 5) Advanatge II Large Dog Application
- 6) Advantage II Large Dog Draft label, dated 11/28/12 (1 copy)
- 7) Advanatge Il Extra Large Dog Application
- 8) Advantage II Extra Large Dog Draft label, dated 11/28/12 (1 copy)



Environmental Protection Agency Weshington, OZ 20480 Amendment Other Application for Pesticide - Section I 1. CompanyProduct Number 11356-128 Application for Pesticide - Section I 1. CompanyProduct Number 11356-128 AccompanyProduct Number 11356-128 Accom	Fieese reed instructions on re	verse before completing form.			(Ferr	n Appro	oved. OMB I	No. 2070-0060	
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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460



NOV 0 7 2012

OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

Douglas Spilker, Ph.D Bayer HealthCare LLC, Animal Health Division P.O. Box 390 Shawnee Mission, KS 66201-0390

Dear Dr. Spilker:

Subject:

Amendment to update labels per spot on mitigation letter sent by the Agency

dated September 30, 2011

EPA Registration Nos./Product name: 11556-125, Advantage II Medium Dog 11556-127, Advantage II Large Dog 11556-128, Advantage II Small Dog 11556-130, Advantage II Extra Large Dog

The labeling referred to above submitted in connection with the Federal Insecticide, Fungicide and Rodenticide, as amended are acceptable.

As a reminder, this registration is time-limited and expires January 17, 2013. You must apply to extend the expiration and/or to change the terms of this registration.

Per the implementation of label changes for pet spot on products, the Agency has reviewed a copy of the print ready label.

A stamped copy of the labeling is enclosed for your records. If you have any questions regarding this label, please contact Autumn Metzger at (703) 305-5314.

Venus Eagle

Product Manager 01

Insecticide-Rodenticide Branch Registration Division (7505P)

Reason To Issue:

Revise according to EPA "Implementation

of Label Changes to Pet Spot-On Products"

document

Date:

09/25/12

Supersedes: 03/26/12 and

09/15/10

NOTE TO REVIEWER: [(Brackets and parentheses indicate alternate language)]

[Front panel]

Advantage® II Small Dog

Once-A-Month Topical Treatment for Fleas and Lice For Use Only on Dogs and Puppies 7 Weeks and Older and Weighing 3 - 10 lbs.

[Selected optional claims bulleted here from page 10 and/or 11]

- ٠
- •
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- ٠

Active Ingredients	% By Weight
1midacloprid	9.10%
Pyriproxyfen	0.46%
Other Ingredients	90.44%
Total	100.00%
EPA Est. 11556-XXX-X EPA Reg. No	. 11556-128

KEEP OUT OF REACH OF CHILDREN

CAUTION

See back panel for Precautionary Statements. For Directions for Use, Storage and Disposal, and First Aid see package insert inside.

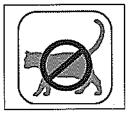
ACCEPTED NOV 0 7 2012

Under the Federal Insecticide, Fungicide, and Rodenticide Act, as amended, for the pesticide registered under:

EPA. Reg. No: 11556-128

DO NOT USE ON CATS

Icon size 1.5cm x 1.5cm



Page 1 of 11

Advantage 11 Small Dog ib.doc

Reason To Issue:

Revise according to EPA "Implementation of Label Changes to Pet Spot-On Products"

document

Date:

09/25/12 Supersedes: 03/26/12 and

09/15/10

[Back Panel]

Advantage® II Small Dog

Once-A-Month Topical Treatment for Fleas and Lice For Use Only on Dogs and Puppies 7 Weeks and Older and Weighing 3 - 10 lbs.

READ THE ENTIRE LABEL BEFORE EACH USE

For the Prevention and Treatment of Flea and Lice Infestations [on Dogs]

PRECAUTIONARY STATEMENTS

HAZARDS TO HUMANS

CAUTION: Harmful if swallowed. Causes moderate eye irritation. Avoid contact with eyes or clothing. Wash hands thoroughly with soap and warm water after handling.

HAZARDS TO DOMESTIC ANIMALS

For external use only. Do not use on puppies under 7 weeks of age or weighing less than 3 lbs. As with any product, consult your veterinarian before using this product on debilitated, aged, pregnant or nursing dogs. Individual sensitivities, while rare, may occur after using ANY pesticide product for dogs. If signs persist, or become more severe, consult a veterinarian immediately. If your dog is on medication, consult your veterinarian before using this or any other product.

Side Effects: Monitor your dog after application. Side effects, although very rare, may include signs of skin irritation such as redness, scratching, or other signs of discomfort. Gastrointestinal signs such as vomiting or diarrhea have also been reported. If these or other side effects (such as lethargy) occur, consult your veterinarian or call 1-800-422-9874.

DO NOT USE ON CATS. Keep cats away from treated dogs for 24 hours. If applied to a cat or ingested by a cat, contact your veterinarian.

1con size 1.5cm x 1.5 cm

For consumer questions call I-800-255-6826. For medical emergencies call 1-800-422-9874.

RESTRICTIONS:

 Use only on dogs 7 weeks and older. Do not apply to puppies or dogs weighing less than 3 lbs. Do not use on other animals.

Revise according to EPA "Implementation Reason To Issue:

of Label Changes to Pet Spot-On Products"

document

Date:

09/25/12 Supersedes: 03/26/12 and

09/15/10

Do not apply more than one (1) tube per treatment.

• Do not have contact or allow children to have contact with treated area until completely dry.

Net Contents: [X] Tube(s) each 0.014 fl. oz. (0.4 mL)

[Sample - Not for (Re)Sale]

Manufactured for Bayer HealthCare LLC Animal Health Division P.O. Box 390 Shawnee Mission, Kansas 66201 USA

Made in Germany

Reason To Issue:

Revise according to EPA "Implementation of Label Changes to Pet Spot-On Products"

document

Date:

09/25/12 Supersedes: 03/26/12 and

09/15/10

[Back Panel and/or Insert]

Advantage® II Small Dog

Once-A-Month Topical Treatment for Fleas and Lice For Use Only on Dogs and Puppies 7 Weeks and Older and Weighing 3 - 10 lbs.

READ THE ENTIRE LABEL BEFORE EACH USE

For the Prevention and Treatment of Flea and Lice Infestations [on Dogs]

DIRECTIONS FOR USE

It is a violation of Federal Law to use this product in a manner inconsistent with its labeling.



HOW TO OPEN

- 1. Being careful not to cut close to the blister cavities, take scissors and cut off one section of the card containing a single tube.
- Take the separated section, and cut into the blister cavity across the small side, close 2. to the cap of the tube.
- Peel off the foil, and take out the tube. 3.
- Repeat steps 1 to 3 for each tube. 4.

HOW TO APPLY

- I. Remove one applicator tube from the package. See "HOW TO OPEN" section.
- Hold applicator tube in an upright position facing away from you and your pet's face 2. and eyes. Pull cap off tube.

[Visuals Depicting How to Open Applicator Tube]

- 3. Turn the cap around and place other end of cap back on tube.
- 4. Twist cap to break seal, then remove cap from tube.
- The dog should be standing for easy application. Part the hair on the dog's back, 5. between the shoulder blades, until the skin is visible. Place the tip of the tube on the skin and squeeze the tube to expel the entire contents directly on the skin. Do not get this product in your dog's eyes or allow your dog to ingest this product. Do not allow the product to run off.

Reason To Issue: Revise according to EPA "Implementation

of Label Changes to Pet Spot-On Products"

document

Date: 09/25/12 Supersedes: 03/26/12 and

09/15/10

[Visuals Depicting Application To Animal]

6. Discard empty tube as described in the Storage and Disposal section.

7. Under normal conditions the product is effective for a month. However, in case of severe flea infestation, retreatment may be necessary earlier than four weeks. Do not retreat more often than once every seven (7) days. After flea control is attained, return to a monthly retreatment schedule.

PRODUCT INFORMATION

The successive feeding activity of fleas on dogs frequently elicits a hypersensitivity skin disorder known as flea allergy dermatitis (FAD) or flea bite hypersensitivity. Treatment of dogs with Advantage® II Small Dog rapidly kills fleas within 12 hours which may reduce the incidence of this condition.

Advantage® 11 Small Dog kills existing fleas on dogs within 12 hours. Reinfesting fleas are killed within 2 hours with protection against further flea infestation lasting for four (4) weeks. Pre-existing pupae in the environment may continue to emerge for six (6) weeks or longer depending upon the climatic conditions.

Fleas, flea eggs, and flea larvae in the dog's environment are killed following contact with an Advantage® II Small Dog treated dog. Advantage® II Small Dog provides multi-stage flea control effectively breaking all flea life-cycle stages for quick and lasting control of flea populations.

Advantage® II Small Dog kills adult fleas quickly, within 12 hours, inhibits the development of immature flea life stages and prevents them from reaching the biting adult stage.

Advantage® II Small Dog kills [(biting) (chewing)] lice that infest dogs and puppies, and prevents further infestations.

Advantage® II Small Dog is waterproof and remains effective following a shampoo treatment, swimming or after exposure to rain or sunlight.

Monthly treatments are required for optimal control and prevention of fleas.

Reason To Issue:

Revise according to EPA "Implementation

of Label Changes to Pet Spot-On Products"

document

Date:

09/25/12 Supersedes: 03/26/12 and

09/15/10

KEEP OUT OF REACH OF CHILDREN

CAUTION

PRECAUTIONARY STATEMENTS HAZARDS TO HUMANS

CAUTION: Harmful if swallowed. Causes moderate eye irritation. Avoid contact with eyes or clothing. Wash hands thoroughly with soap and warm water after handling.

	FIRST AID			
If Swallowed:	 Call a poison control center or doctor immediately for treatment advice. Have person sip a glass of water if able to swallow. Do not induce vomiting unless told to do so by the poison control center or doctor. Do not give anything to an unconscious person. 			
If In Eyes: • Hold eye open and rinse slowly and gently with water for 1. 20 minutes. Remove contact lenses, if present, after the first minutes, then continue rinsing eye. • Call a poison control center or doctor for treatment advice.				
If On Skin	Wash with plenty of soap and water.			
	HOT LINE NUMBER			
	ner or label with you when calling a poison control center or doctor, For medical emergencies call 1-800-422-9874. For consumer 5-6826.			
	NOTE TO PHYSICIAN			
Treat the patient sympto	matically.			

HAZARDS TO DOMESTIC ANIMALS

For external use only. Do not use on puppies under 7 weeks of age or weighing less than 3 lbs. As with any product, consult your veterinarian before using this product on debilitated, aged, pregnant or nursing dogs. Individual sensitivities, while rare, may occur after using ANY pesticide product for dogs. If signs persist, or become more severe, consult a veterinarian immediately. If your dog is on medication, consult your veterinarian before using this or any other product.

Side Effects: Monitor your dog after application. Side effects, although very rare, may include signs of skin irritation such as redness, scratching, or other signs of discomfort. Gastrointestinal signs such as vomiting or diarrhea have also been reported. If these or other side effects (such as lethargy) occur, consult your veterinarian or call I-800-422-9874.

Reason To Issue: Revise according to EPA "Implementation

of Label Changes to Pet Spot-On Products"

document

Date:

09/25/12 Supersedes: 03/26/12 and

09/15/10

DO NOT USE ON CATS. Keep cats away from treated dogs for 24 hours. If applied to a cat or ingested by a cat, contact your veterinarian.

Icon size 1.5cm x 1.5 cm



For consumer questions call 1-800-255-6826. For medical emergencies call 1-800-422-9874.

RESTRICTIONS:

- Use only on dogs 7 weeks and older. Do not apply to pupples or dogs weighing less than 3 lbs. Do not use on other animals.
- Do not apply more than one (1) tube per treatment.
- Do not have contact or allow children to have contact with treated area until completely dry.

STORAGE AND DISPOSAL

Do not contaminate water, food or feed by storage or disposal.

Pesticide Storage: Store in a cool, dry place inaccessible to children and pets. Pesticide Disposal and Container Handling: Nonrefillable container. If empty: Do not reuse or refill this container. Place in trash or offer for recycling if available. If partly filled: Call your local solid waste agency or 1-800-422-9874 for disposal instructions. Never place unused product down any indoor or outdoor drain.

LIMITED WARRANTY AND LIMITATION OF DAMAGES

Bayer HealthCare LLC, Animal Health Division warrants that this material conforms to the chemical description on the label. TO THE EXTENT CONSISTENT WITH APPLICABLE LAW, BAYER MAKES NO OTHER EXPRESS OR IMPLIED WARRANTY, INCLUDING ANY OTHER EXPRESS OR IMPLIED WARRANTY OF FITNESS OR MERCHANTABILITY, and no agent of Bayer is authorized to do so except in writing with a specific reference to this warranty. To the extent consistent with applicable law, any damages arising from a breach of this warranty shall be limited to direct damages and shall not include consequential commercial damages such as loss of profits or values, etc.

Reason To Issue:

Revise according to EPA "Implementation of Label Changes to Pet Spot-On Products"

document

Date:

09/25/12 Supersedes: 03/26/12 and

09/15/10

[Label on Individual Tube]

Advantage® II Small Dog

9.10% Imidacloprid

0.46% Pyriproxyfen

0.014 fl. oz. (0.4 mL)

EPA Reg. No. 11556-128

Keep Out of Reach of Children

CAUTION

Read The Entire Label Before Use

BAYER

Lot No. 0000000

Reason To Issue: Revise according to EPA "Implementation

of Label Changes to Pet Spot-On Products"

document

Date:

09/25/12 Supersedes: 03/26/12 and

09/15/10

[Label on blister card; one card containing 1, 2, 3, 4, 5 or 6 tubes]

Advantage® II Small Dog

For external use only on dogs and puppies 7 weeks and older and weighing 3 - 10 lbs.

9.10% Imidacloprid

0.46% Pyriproxyfen

[X] - 0.014 fl. oz. (0.4 mL)

EPA Reg. No. 11556-128

BAYER



Reason To Issue: Revise according to EPA "Implementation

of Label Changes to Pet Spot-On Products"

document

Date: 09/25/12 Supersedes: 03/26/12 and

09/15/10

NOTE TO REVIEWER: [(Brackets and parentheses indicate alternate language)]

OPTIONAL MARKETING CLAIMS

- For use on dogs and puppies 7 weeks of age and older
- Advantage II contains [imidacloprid], and [an/the] [insect growth regulator] [IGR]
 [pyriproxyfen]
- A single topical application remains effective for [4 weeks] [a month]
- Convenient, easy-to-apply topical solution
- Convenient, easy-to-apply and fragrance free [monthly] [topical solution]
- Once a month topical flea treatment for dogs 7 weeks of age or older
- Advantage II is indicated for the prevention and treatment of fleas on dogs
 7 weeks of age and older
- For the treatment and prevention of flea [and lice] infestations
- One treatment prevents further flea infestations for [4 weeks] [a month]
- Kills fleas on dogs within [12] hours and continues to prevent infestations for [four weeks] [a month]
- Kills fleas before they lay eggs
- Larval flea stages in the dog's environment are killed following contact with an Advantage II treated dog
- Kills larval stages of fleas in the dog's environment
- Kills fleas within [12] hours of application
- Stops existing flea infestations by killing adult fleas
- Prevents [Stops] reinfestations by killing adult fleas before they lay eggs
- [Prevents] [Stops] flea eggs from hatching [into biting adults]
- Effectively breaks the flea life cycle
- Effectively targets all [life] stages of [fleas]
- [Kills] [Controls] all flea life stages
- 3-way flea protection ([kills] [controls] adults, larvae, and eggs)
- [Prevents] [Stops] flea eggs [and flea larvae] from developing into [(biting) (adult)] fleas
- Treatment with Advantage II rapidly kills fleas which may cause flea allergic dermatitis [FAD] or flea bite hypersensitivity
- Flea adulticide, larvicide, and ovicide
- Kills flea eggs
- Controls highly [irritating] [annoying] [flea] [insect] bites
- Controls flea problems
- Provides flea protection
- Controls existing fleas and flea eggs [(plus) (and)] [prevents] future flea infestations in the home

Reason To Issue: Revise according to EPA "Implementation

of Label Changes to Pet Spot-On Products"

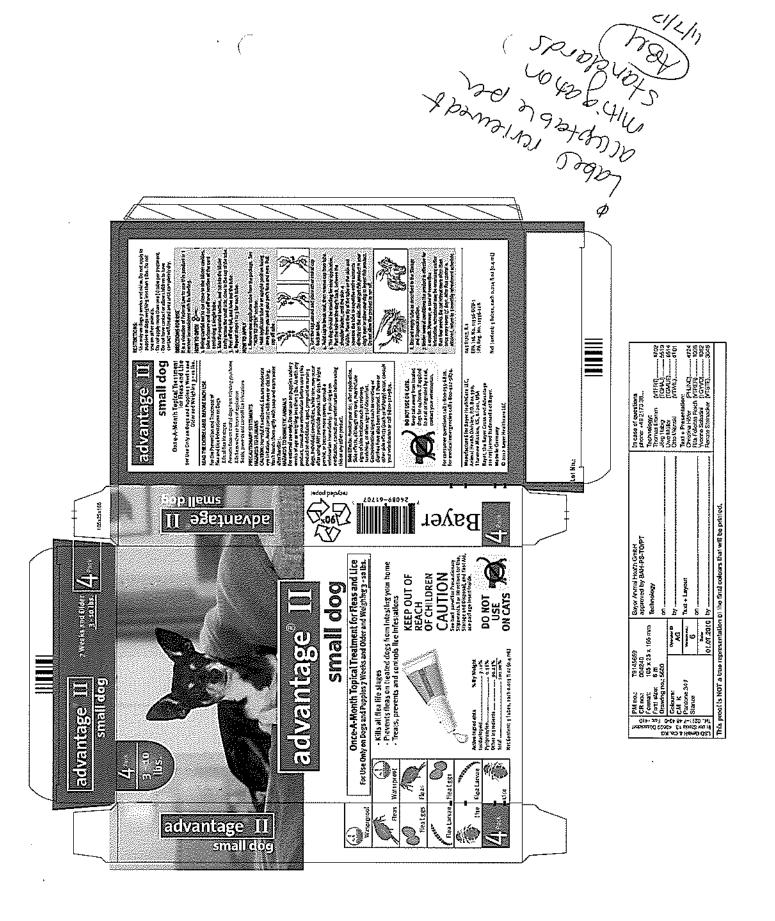
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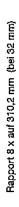
Date:

09/25/12 Supersedes: 03/26/12 and

09/15/10

- Starts working through contact
- Use flea [prevention][protection] year-round
- Contains an insect growth regulator (IGR) to kill flea eggs and prevent reinfestation
- Monthly use of Advantage II kills fleas which may cause ([flea allergy dermatitis][flea bite hypersensitivity])
- Multi-stage flea control
- Prevents fleas on treated dogs from infesting (reinfesting) your home
- Kills fleas which may serve as intermediate hosts for tapeworms
- Kills [(biting) (chewing)] lice
- For treatment and prevention of [(biting) (chewing)] lice [infestations]
- Stops existing [(biting) (chewing)] lice infestations
- Dual protection against fleas and lice
- Treats, prevents and controls [(biting) (chewing)] lice [infestations]
- Provides effective control of [(biting) (chewing)] lice [infestations]
- Kills [(biting) (chewing)] lice and prevents further infestations
- For treatment and prevention of infestations with [(biting) (chewing)] lice
- Remains effective after bathing and/or swimming
- Remains effective following swimming and/or shampooing
- Waterproof
- Remains effective after exposure to rain or sunlight
- Fragrance-free
- [In child-resistant packaging]







Rapport 3 x auf 210 mm

충유				Bayer Animal Health GmbH approved by BAH-PS-TO/PT	In case of questions phone: +49 2173 38
KG - 40589 Dücs 49-0 · Fax: -4	Format: Font sizo: Drawing no.	285 mm 6 pl .: 9949		Technology	Technology: Thomas Fromm (VTFRT)4702 Jörg Habig (TGHAJ)5518
0 5 8	Colours: Schwarz		Operator ID AG	by	Uwe Müller (TGMUE)4614 Otto Wilnski (VTWIL)4701 Text + Presentation:
LSD GmbH In dor Steads Tel.: 0211-7	Stanze		Version no.: 4	Tox1 + Layou1 on	Christina Höfer (PHJNC)
Tel.			18.06.2010	by	Yvonne Sabatini (TGYVÖ)4082 Renate Steinacker (VTSTE)3046
This p	oof is NOT	a fruo rep	presentation	of the final colours that will be printed.	

advantage® II

small dog

Once-A-Month Topical Treatment for Fleas and Lice Tor Use Only on Pogs and Pupples 7 Weeks and Older and Welghing 3 - 20 lbs.

READ THE ENTIRE LABEL BEFORE EACH USE.

- For the Prevention and Treatment of Flez and Line Intestations on Dogs
- Kills all flea ille stages
- Prevents fleas on treated dogs from intesting your home One treatment prevents further flea infestations for a month
- Kills fleas on dogs within sa hours of application
- Treats, prevents and tontrols lice intestations
- Waterproof
- Fragrance-free

Active Ingrodients

% By Weight 9.10%

Pyriproxyfen...... Other ingredients...

...0.46%

Statements.

DIRECTIONS FOR USE

It is a violation of Federal Law to use this product in a manner inconsistent with its labeling.

NOW TO OPEN 冬

- Being careful not to cut close to the bilster cavities, take scissors and cut off one section of the card containing a single tube.
- a. Take the separated section, and cut into the blister cavity across the small side, close to the rap of the tube.
- 3. Peel off the foil, and take out the tube. 4. Repeat steps r to 3 for each tube.

HOW TO APPLY

- s. Remove one applicator tube from the package.

 See "HOW TO OPEN" section.
- a. Hold applicator tube in an upright position facing away from you and your pet's lace and eyes. Pult cap off tube.







- 3. Turn the cap around and place other end of cap
- Twist cap to break seal, then remove cap from tube.
- Touch.

 The dog should be standing for easy application. Part the hair on the dog's back, between the shoulder blades, until the skin Is visible. Place the tip of the tube on the skin and squeeze the tube to expel the entire contents directly on the skin. Po not get this product in your dog's eyes or allow your dog to ingest this product. Do not allow the product to run off.





- Discard empty tube as described in the Storage and Pisposal section.
- 7. Under normal conditions the product is effective for a month. However, in case of severe flea infestation, retreatment may be necessary earlier than four weeks. Do not retireat more often than once every seven (y) days. After flea control is attained, return to a monthly retreatment schedule.

PRODUCT INFORMATION

The sucressive feeding activity of fleas on dogs frequently clicits a hypersensitivity skin disorder known ar flea allergy demastich (FAD) or flea bite hypersensitivity. Freatment of dogs with Advantage IL Small Dog rapidly kills fleas within 12 hours which may reduce the incidence of this condition.

Advantage II Small Dog kitts existing fleas on dogr within sa hours. Reinfesting fleas are killed within a hours with protection against further fleat infestation lasting for four (4) weeks. Pro-existing pupase in the environment may continue to emerge for six (6) weeks or longer depending upon the climatic conditions.

Fleas, flea eggs, and flea larvae in the dog's environment are killed following rontact with an Advantage It Small Dog treated dog. Advantage It Small Dog provides multi-stage flea control effectively breaking all flea fle-cycle stages for quick and lasting control of flea populations.

Advantage tt Smatt Dog kitts adult fleas qutckly, within 12 hours, inhibits the development of Immature flea tile stages and prevents them from reaching the biting adult stage.

Advantage II Small pog kills chewing lice that Infest dogs and pupples, and prevents further infestations.

Advantage II Small Pog is waterproof and remains effective following a shampoo treatment, swimming or after exposure to rain or sunlight. Monthly treatments are required for optimal control and prevention of fleas.

KO KO Dies 0 - Faz: 4	PM no.: CR no.: Format: Font size: Orawing no.:	79r458: 004240; 148 x 21 9 pt	004247 07 mm	Bayer Animal Heath GrapH approved by BAH-PS-TO/PT Technology	in case of question phono: +49 2 (73) Fechnology: Thomas Fromm Jorg Fisting One Müter	
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	Stanze		Version sq.:	Text + Layout	Text + Presentation Cariatina Héler Rita Folicitas Reich	onc [PHLINC]
3 4 3			09.07.2010	by	Yvonno Sabatni Panate Stoinacker	(TGYVO)
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KEEP OUT OF REACH OF CHILDREN CAUTION

PRECAUTIONARY STATEMENTS HAZARDS TO HUMANS

CAUTION: Harmfulif swallowed, Causes moderate eye imitation. Avoid contact with eyes or clothing. Wash hands thoroughly with soap and warm water after handling.

FIRST AID Call a poison control center or doctor immediately for Beatment advice. Have person slp a glass of water if able to swallow.

Do not induce vomiting unless told to do so by the poison control renter or doctor. Do not give anything to an unconscious person. If in Eyes: Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact tenses, it present, after the first 5 minutes, then continue rinsing eye. Call a poison control center or doctor for treatment advice. ∦f On Skin Wash with plenty of soap and water.

Have the product container or label with you when calling a poison control center or doctor. or going for treatment. For medical emergencies call s-800-422-9874. For consumer questions call c-800-255-6826.

HOTEINEHUMBER

NOTE TO PHYSICIAN

Treat the patient symptomatically

HAZARDS TO COMESTIC ANIMALS

For external use only. Po not use on pupples under 7 weeks of age or weighing less than 3 lbs. As with any product, consult your veterinarian before using this product on debilitated, aged, pregnant or nursing dogs, individual sensitivities, while rare, may occur after using ANY pesticide product tor dog c.

If signs persist, or become more severe, consult a veterinarian immediately. It your dog is on medication, consult your veterinarian before using this or any other product.

Side Effects: Monitor your dog after application. Side effects, although very rare, may include signs of skin irritation such as redness. scratching, or other signs of discomfort. Stratumer, or other agrics or occommen, Gastrointestinal signs such as vomiting or diarrhea have also been reported. If these or other side effects (such as lethargy) or ruc consult your veterinarian or call 6800-822-9874.



DO NOT USE ON CATS, Keep cats away from treated dogs to 24 hours, I (applied to a cat or ingested by a cal, contact your 3 veterinarian.

For consumer questions calls:800-255-68 c6. For medical emergencies call 5-800-422-9874.

RESTRICTIONS:

- Use only on dogs 7 weeks and older. Do not apply to puppies or dogs weighing less than 3 lbs. Do not use on other animals.
- Do not apply more than one (1) tube per treatment.

Do not have contact or allow children to have contact with treated area until completely dry.

STORAGE AND DISPOSAL

o noccontaminate water, food or feed by storage or disposal.

Posticide Storage: Store in a cool, dry place naccessible to children and pets. esticide Disposal and Container Handling: ionrefillable container.

t empty: Do not reuse or refit this container. Place in trash or offer for recycling if available. it partly filled: Call your local solid waste agency or s-800-422-9874 for disposatinstructions. lever place unused product down any indoor or utdoor drain.

LIMITEO WARRANTY AND LIMITATION OF DAMAGES

Bayer Health Care LLC, Animal Health Division warrants that this material conforms to the chemical description on the labet, TO THE EXTENT.
CONSISTENT WITH APPLICABLE LAW, BAYER MAKES NO OTHER EXPRESS OR IMPLIED WARRANTY, INCLUDING ANY OTHER EXPRESS OR LAPLIED WARRANTY OF FITNESS OR MERCHANTABILITY, and no agent of 8ayer is authorized to do so except in writing with a specific reference to this warranty. To the extent consistent with applicable law, any damages arising from a breach of this warranty shall be limited to direct damages and shall not include consequential commercial damages sur has loss of profits or vatues, etc.

Manufactured For Bayer HealthCare LLC, Animal Health Division P.O. Box 390, Shawnee Mission, Kansas 66201 USA EPA Reg. No. 51556-128 Bayer, the Bayer Crost and Advantage are registered trademarks of Bayer. © 2012 Bayer HealthCare LLC

Advantage II is protected by the following U.S. patents: 6,232,328 and 6,001,858

B3000539/04461707/04461715, R.S EPA Est. No. 17556-DEU-1

Bayer

1 37	PM na.: CR no.: Format Font size: Drawing no.:	79 (456) 00-4240, (66 x 2) 9 pt	004247	Bayer Animal Hooth Gnich approved by BAH-PS-TO/PT Technology	In case of question phone: +49 2173; 7echnology: Thomas fromm Jörg Habig Uwa Miller	
1.50 Gmb/1 & Co, KG h Gw Stech (3 - A05/81) kd. (Q.11-7 48 49-0 - Fa	Colours: Schwarz Stanze		AG Ward a mad 8 Date: 09.07.2010	by	Otto Wänski Text + Presentatk Christha Höfer Rita Felicitas Reich Yvenne Sabatin	(VTWL) 4701
This p	roof is NOT :	a truo no	prosentation	of the final colours that will be printed.		



Advantage II Dog master Labels (11556-125, -127, -128, -130) - Revised Doug Spilker

to:

Autumn Metzger 10/22/2012 04:42 PM

Hide Details

From: Doug Spilker <doug.spilker@bayer.com>

To: Autumn Metzger/DC/USEPA/US@EPA

History: This message has been forwarded.

8 Attachments



Advantage II Extra Large Dog ib highlighted.pdf Advantage II Extra Large Dog ib.pdf



Advantage II Large Dog ib highlighted.pdf Advantage II Large Dog ib.pdf



Advantage II Medium Dog ib highlighted.pdf Advantage II Medium Dog ib.pdf



Advantage II Small Dog ib highlighted.pdf Advantage II Small Dog ib.pdf

Hi Autumn,

Please find attached the draft master labels (1 clean copy; 1 highlighted copy), text dated 9/25/2012, for the Advantage II Small Dog (11556-128), Advantage II Medium Dog (11556-125) and Advantage Il Large Dog (11556-127), and Advantage II Extra Large Dog (11S56-130.) The following are the text changes that were made from the last version; you will notice that these are basically the same as the previously submitted cat labels except for the last line item.

All of the elements of the Final Printed Labeling (facsimile) for these products will be sent under separate emails by product.

Page	Changes to Master label
Page 1	Updated text date to 9/25/12; updated version designation from "ia" to "ib" – see file name.
Page 1	Changed referral statement to show that First Aid appears inside on insert. This was agreed to in email of 8/24/12 (A. Metzger to D. Spilker).
Page 2	First Aid removed, and moved to page 6 (insert).
Page 6-7	Added First Aid section and <i>duplicated</i> Precautionary Statements, Hazards et al. (from page 2) so that it will match the insert of the Final printed labeling.
5mail Dog Label Only (11556-128)	Changed throughout the label the minimum weight from 3½ lb. to 3 lb. based on DER, dated 10/10/2012 (Decision No. 463857).

Look forward to seeing you on Wednesday.

Best Regards, Doug

Douglas A. Spilker, Ph.D. Manager - EPA Reg. Affairs BAYER HEALTHCARE LLC Animal Health Division Office: 913-268-2751

Mobile: 816-506-3102

Email: doug.spilker@bayer.com

Address: P.O. Box 390

Shawnee Mission, KS 66201-0390

Country: USA

Bayer Animal Health "Protecting.Curing.Caring...Together"

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For allemate tanguages please go to http://bayerdisclaimer.bayenveb.com



RE: Advantage II Cat Labels (11556-150, -151 and -152) Doug Spilker to: Autumn Metzger

Cc: Angela Mall, Venus Eagle

09/24/2012 11:24 AM

History:

This message has been replied to and forwarded.

Good Morning Autumn,

They are working on these package labels to try and meet your deadline. However, they are having trouble fitting all of the new information on the back panel – e.g. new Restrictions section, side effects et al. We would like your permission to move the First Aid section to the insert (and of course change the referral statement to reflect this.) The Precautionary Statements (Hazard to Humans, Hazard to Domestic Animals, Side Effects, and Restrictions would appear on the back panel.) ALL of this information would also be repeated in its entirety on the insert, so the insert is very complete – including all the proper positioning of the First Aid statements with the Precautionary statements.

As I read the LRM (7-10), it says that the Agency may permit reasonable variations in placement of the First Aid statements as long as the referral statement appears on the front panel. We feel this is a reasonable request, and does not increase any potential hazard in using the product.

We ask for your permission to do this. If you need revised Master labels to reflect this change, please let me know and we will fix it.

Best Regards, Doug

Douglas A. Spilker, Ph.D. Manager - EPA Reg. Affairs BAYER HEALTHCARE LLC Animal Health Division Office: 913-268-2751

Office: 913-268-2751 Mobile: 816-506-3102

Email: doug.spilker@bayer.com

Address: P.O. Box 390 Shawnee Mission, KS 66201-0390 Country: USA

Bayer Animal Health "Protecting.Curing.Caring...Together"

From: Autumn Metzger [mailto:Metzger.Autumn@epamail.epa.gov]

Sent: Tuesday, September 18, 2012 2:03 PM

To: Doug Spilker

Subject: Re: Advantage II Cat Labels (11556-150, -151 and -152)

Hi Doug,

These all look ok. Please go ahead and use these to update the final printed labeling for each and submit to me via email (if possible). We cannot close these out without that part (since I have to be sure the font sizes/colors/pictures and everything else are adequately translated to the final printed labeling). Can we shoot for this back to me within 3 weeks? We'll have to have this closed out before we can finish up the ferret amendment and we would rather not push that back.

Autumn Metzger Biologist U.S. Environmental Protection Agency Insecticide-Rodenticide Branch Registration Division (7505P) 1200 Pennsylvania Ave. NW Washington, DC 20460

Tel: 703 305-5314 Fax: 703 308-5433

Email: metzger.autumn@epa.gov

Doug Spilker ---09/07/2012 07:47:47 AM---Hi Autumn, Here's your welcome back present. Attached are the revised labels for the cat products wi

From: Doug Spilker <doug.spilker@bayer.com>
To: Autumn Metzger/DC/USEPA/US@EPA
Co: Venus Eagle/DC/USEPA/US@EPA

Date: 09/07/2012 07:47 AM

Subject: Advantage II Cat Labels (11556-150, -151 and -152)

Hi Autumn,

Here's your welcome back present. Attached are the revised labels for the cat products with the changes you requested. I have looked at these ad nauseam, and I hope I fixed everything. The Advantage II dog labels will be in a separate email. I am in the office next week on Monday, and Friday, but in DC Tuesday thru Thursday. I'm haping we don't, but let me know if we need to work on these some more.

Best Regards, Doug

Douglas A. Spilker, Ph.D. Manager - EPA Reg. Affairs BAYER HEALTHCARE LLC Animal Health Division Office: 913-268-2751 Mobile: 816-506-3102

Email: doug.spilker@bayer.com

Address: P.O. Box 390 Shawnee Mission, KS 66201-0390 Country: USA

Bayer Animal Health "Protecting.Curing.Caring...Together"



Advantage II Dog Labels (11556-125, -127, -128, -130)

Doug Spilker

to:

Autumn Metzger 09/07/2012 07:47 AM

Cc:

Venus Eagle Hide Details

From: Doug Spilker <doug.spilker@bayer.com>

To: Autumn Metzger/DC/USEPA/US@EPA

Cc: Venus Eagle/DC/USEPA/US@EPA

4 Attachments







Advantage II Extra Large Dog ia.pdf Advantage II Large Dog ia.pdf Advantage II Medium Dog ia.pdf



Advantage II Small Dog ia.pdf

For your review.

Best Regards, Doug

Douglas A. Spilker, Ph.D. Manager - EPA Reg. Affairs BAYER HEALTHCARE LLC Animal Health Division

Office: 913-268-2751 Mobile: 816-506-3102

Email: doug.spilker@bayer.com

Address: P.O. Box 390

DATA PACKAGE BEAN SHEET

Date: 03-Oct-2012 Page 1 of 1 Decision #: 463857

DP #: (405723)

NON PRIA

Parent DP #:

Submission #: 924809

E-Sub #:

* * * Registration Information * * *

Registration:	11556-128 - ADVANTAGE II	SMALL DOG	380 229 #31229
	11556 - BAYER HEALTHCARE LLC		
	RM 01 - Venus Eagle - (703) 308-80		
	Autumn Metzger AMETZGER		
		PRIA Due Date: 06-Dec-2012	Edited Due Date:
Type of Registration;	Product Registration - Section 3		
Action Desc:	(300) LABEL REVISION; NO DATA	REQUIRED;	
tngredients:	129099, Imidacloprid(9.1%)		
	129032, Pyriproxyfen(.46%)		
	* * * Data F	Package Information *	
Expedite:	Yes No	Date Sent: 03-Oct-2012	Due Back:
DP tngredient:	129099, Imidacloprid		
	129032, Pyriproxyfen		
DP Title:	Companion Animat minimal weight	check	
CSF Included:		ided; O Yes O No Parer	nt DP #:
Assigned T	<u>o</u>	Date In Date Out	Ct 24,2012
Organization: RD / T	TR8		Last Possible Science Due Date: 27.May-2017
			Science Due Date:
			Sub Data Package Due Date:
	* * * Studies * * * Additional Data F	Sent for Review * * * No Studies	ion*** PIS type UP SOF
	No Additi	onal Data Packages	Show of the
	* * * Data Baal	kage Instructions * * *	12 Jan 03
Byron: Please verify the requirements.		J	review. This is 10 fulfill the spot-on mitigation
1hanks			anr

autumn



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

OFFICE OF PESTICIDE PROGRAMS REGISTRATION DIVISION (7505P)

October 10, 2012

MEMORANDUM: Minimum Treatment Weight and Age for EPA Reg. No. 11556-128

Subject:

Name of Pesticide Product: ADVANTAGE II SMALL DOG

DP Barcode:

EPA Reg. No. /File Symbol: 11556-128 DP 405723

Decision No.:

463857

Action Code:

300

PC Codes:

129099 (Imidacloprid: 9.1%)

129032 (Pyriproxyfen: 0.46%)

From:

Byron T. Backus, Ph.D., Toxicologist

Byon T. Bale EMcDulus Oct -10-2012 Oct. 10,2012

Technical Review Branch Registration Division (7505P)

To:

Autumn Metzger/Venus Eagle RM 01

Insecticide-Rodenticide Branch Registration Division (7505P)

Registrant:

BAYER HEALTHCARE LLC

FORMULATION FROM LABEL:

Active Ingredient(s):		<u>by wt.</u>
129099 Imidacloprid		9.10%
129032 Pyriproxyfen		0.46%
Other Ingredient(s):		90.44%
	TOTAL	100.00%

ACTION REQUESTED: The Risk Manager requests:

"...Please verify the lowest weight allowed for this size product based on their original CA review. This is to fulfill the spot-on mitigation requirements..."

BACKGROUND:

The companion animal safety studies that supported the registration of EPA Reg. No. 11556-128 are a puppy study in MRID 45097101 (Abraham, A. (2000) Evaluation of the General Safety of 9.1% (w/w) Imidacloprid with 0.9% (w/w) Pyriproxyfen Spot-on Formulation in the Target Species, Seven Week Old Puppies: Lab Project Number: 75119. Unpublished study prepared by Bayer Corporation. 147 p. {OPPTS 870.7200}) and an adult dog study in MRID 45097102 (Abraham, A. (2000) Evaluation of the General Safety of 9.1% (w/w) Imidacloprid with 0.9% (w/w) Pyriproxyfen Spot-on Formulation in the Target Species, Adult Dog: Lab Project Number: 75121. Unpublished study prepared by Bayer Corporation. 130 p. {OPPTS 870.7200}). The last accepted (September 27, 2010) label indicates that this product (packaged in small tubes containing 0.014 fl. oz. or 0.4 mL formulation) is for once-a-month topical treatment for fleas and lice on dogs and puppies 7 weeks and older and weighing 10 lbs. and under.

COMMENTS AND RECOMMENDATIONS:

1. The following are excerpts from the executive summary of the review (TXR 5001580; EPA File Symbol: 11556-REI, memorandum dated September 8, 2000) of the companion animal safety (beagle puppy) study in MRID 45097101:

In a companion animal safety study (MRID 45097101), Advantage Plus® for Dogs (Active Ingredients: 9.1% Imidacloprid w/w; 0.9% Pyriproxyfen w/w) was applied topically at a dose of 2.0 mL/puppy (5X the label specified dose of 0.4 mL/puppy for puppies ≤10 lbs) to a group of 7 male and 7 female beagle puppies, seven weeks of age at the time of first treatment. Individual weights of the puppies in the treatment group ranged from 2.54 to 4.01 lbs (1.15-1.82 kg) on day -1. Controls (7M, 7F; weight range: 2.49-5.03 lbs; 1.13-2.29 kg) were dosed with the vehicle alone at a dose of 2.0 mL/puppy (5.6X the volume of the vehicle present in the specified dose). Both groups were treated on study days 0, 7, 14, and 21. The recommended label dose is once a month. However, the labeling for these products includes the statement: "If re-treatment becomes necessary earlier than four weeks, do not re-treat more than once weekly."

...Despite the fact that the puppies may not have been entirely free of infection, and despite some deficiencies in the reporting of the data, the study is classified as **Acceptable** as a companion animal safety study (OPPTS 870.7200) in puppies. The lack of any indications of a consistent toxicological response following exposures (a total of 4) to 5X label-specified use applications of the test material indicates that an adequate safety margin exists for this formulation and its proposed use on puppies 7 weeks of age and older.

2. As noted above, the individual weights of the puppies in the treatment group ranged from 2.54 to 4.01 lbs (1.15-1.82 kg) on day -1. From data on pages 30 and 32 of MRID 45097101, the mean weight of the 7 males was 3.44 ± 0.39 lbs, while the mean weight of the 7 females was 3.06 ± 0.45 lbs. However, the 870.7200 Guidelines specify 6 animals/sex, so if the heaviest male and female are excluded, then the mean weight of the remaining 6 males was

- 3.34 ± 0.32 lbs, while the mean weight of the remaining 6 females was 2.92 ± 0.28 lbs (the mean weight of these 6 males and 6 females was 3.13 ± 0.36 lbs). Based on these considerations, we can accept 3 lbs as the lowest minimum weight.
- 3. Individual puppy ages are reported on page 27 of MRID 45097101. The ages of the puppies on the day of first dosing ranged from 6 weeks and 5 days to 7 weeks and 0 days. We can accept 7 weeks as the minimum age.

Bayer HealthCare Animal Health



Via Federal Express - Express Saver

December 9, 2010

Document Processing Desk
Office of Pesticide Programs (7504P) - NonPRIA
U.S. Environmental Protection Agency
Room S-4900, One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202-4501

Attention:

Ms. Venus Eagle/PM 01

Subject:

Advantage II Small Dog (EPA Reg. No. 11556-128) Advantage II Medium Dog (EPA Reg. No. 11556-125) Advantage II Large Dog (EPA Reg. No. 11556-127)

Advantage II Extra Large Dog (EPA Reg. No. 11556-130)

Bayer HealthCare LLC Animal Health P.O. Box 390

Shawnee Mission, KS 66201-0390

Dear Ms. Eagle:

Reference is made to the current registrations of the subject products. One of the conditions of acceptance of the subject registrations is that "[We] must provide the Agency with a projected release for shipment at least 30 days in advance."

Therefore, we are hereby notifying the Agency that our first anticipated shipment of product will be on or after January 17, 2011.

If you have any questions, please do not hesitate to call (913-268-2751).

Sincerely,

Douglas A. Spilker. Ph. D.

Manager, EPA Regulatory Affairs

Doug.Spilker@Bayer.com

Cc: K. Davis (EPA) - email



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY WASHINGTON, D.C. 20460

April 16, 2012

OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

DR. BRUCE MARTIN
BAYER HEALTHCARE LLC
ANIMAL HEALTH DIVISION
PO Box 390
SHAWNEE MISSION, KS 66201-0390

PRODUCT NAME: ADVANTAGE II SMALL DOG COMPANY NAME: BAYER HEALTHCARE LLC

OPP IDENTIFICATION NUMBER: EPA FILE SYMBOL: 11556-128 EPA RECEIPT DATE: 04/12/12

SUBJECT: RECEIPT OF AMENDMENT

DEAR REGISTRANT:

The Office of Pesticide Programs has received your application for an amendment and it has passed an administrative screen for completeness.

During the initial screen we determined that the application appears to qualify for fast track review. The package will now be forwarded to the Product Manager for review to determine its acceptability for fast track status.

If you have any questions, please contact Registration Division, Risk Management Team 1, at (703) 308-8045.

Sincerely,

Y. J. Monne
Front End Processing Staff
Information Services Branch
Information Technology & Resources Management Division

Fee for Service {915171É~

This package includes the following	for Division
New Registration• Amendment□ Studies?□ Fee Waiver?□ volpay% Reduction:	○ AD ○ BPPD ○ RD Risk Mgr. 1
Receipt No. S- EPA File Symbol/Reg. No. Pin-Punch Date:	915171 11556-128 4/12/2012
This item is NOT subject to Action Code: Requested: Granted: Amount Due: \$	Parent/Child Decisions:
Inert Cleared for Intended Use Reviewer: Remarks:	Uncleared Inert in Product Date: 4/13/12—

Please read instructions on reverse bet	ore compliaing form.			` Fo	rm Approved, OMB No. 2070-0060		
0 ED4	United States		☐ Registr	ation	OPP Identifier Number		
EPA EN	/ironmental Protection	n Agency	⊠ Amend				
	Washington, DC 204			ment			
	YVashington, DO 204		☐ Other:				
	Application		ide - Section	ıl			
1. Company/Product Number		2. EPA Produ	-	'	Proposed Classification		
11556-128 4. Company/Product (Name)		Venus Eagl	<u>.e</u>				
Advantage II Small Dog		1			None Restricted		
Name and Address of Applicant (Include ZIP Code)		ed Review. In	accordance w	ith FIFRA Section 3(c)(3)		
Bayer HealthCare LLC, An					composition and labeling		
PO Box 390		to:					
Shawnee Mission, KS 6620.	l .	EPA Reg. I	No	····			
Check if this is a new a	ddress	Product Na	ame				
		Section -	, ,,,				
Amendment – Explain below.			Finat printed lab	els in response to	Agency tetter dated		
Resubmission in response to /	Agency letter dated	[] "Me Too" Applica				
Notification - Exptain below.			Other - Explain I	below			
Explanation:				• • •			
NON-PRIA ACTION (AMEND							
Enclosed for Agency acceptanc							
the EPA "Implementation of La				/30/11 (Received	1 10/I t/11), and other minor		
word and format changes. Final	Printed Labeling for this	product is also	enclosed.				
	········	Section -	<u> </u>	-			
t. Material This Product Will Be Pa			Maria Califolia Dani	:	O. T. and Containing		
Child-Resistant Packaging	Unit Packaging Yes	ļř	Vater Soluble Paci Yes	kaging	Type of Container Metal		
L Yes*	No No		=		Plastic		
L_i No		No. per	No ["Yes"	No. per			
*Certification must			ackage wgt.	container	Glass		
					Paper		
be submitted	olion 4 Sizo(n) 5	tetail Container		5 Looption of	Other (Specifiy) Labet Directions		
Location of Net Contents Inform Label	ntainer 4. Size(s) R	eran Containei		On Label	Labet Directions		
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6. Manner in Which Label is Affixe	d to Product Lithogra	anh	Other_		ig accompanying product		
o. Mainer in willon Laborio Mina.	Paper 9						
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		Section -	IV				
f. Contact Point (Complete items d	irectly below for identificalion	of individual to be	e contacted, if nec	essary, to process	this application)		
Name Title Telephone No. (Include Area							
Douglas A. Spilker, Ph.D. Manager, EPA Regulatory Affairs Code) 913-268-2751							
	Certification 6. Date Application						
I certify that the statements I have made on this form and all attachments thereto are true, accurate and complete. I Received					1		
acknowledge that any knowingly ta under applicabje aw.	acknowledge that any knowingly false or misleading statement may be punishable by fine or imprisonment or both (Stamped)						
2. Signature	1 . A T 3	<u> </u>		4.6.4.			
6/2//	6 1/2 1°	3. Title Manager, EPA Regulatory Affairs					
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4. Typed Name		i. Date	pul 2		6. e. o e.		
Bouglas A. Spilker		7 /1,	put 2	@	e enegre		

(doug.spiker@bayer.com)

EPA Form 8570-1 (Rev. 8-94) Previous editions are obsolete

White- EPA File Copy (original) Yellow-Applicant Copy

ATTACHMENT FOR APPLICATION FOR PESTICIDE REGISTRATION April 5, 2012

Advantage II Small Dog (EPA Reg. No. 11556-128)

Please find enclosed for the Agency's review and acceptance revised draft labeling, dated 03/26/12, for the subject product. Many of the revisions are in response to the EPA "Implementation of Label Changes to Pet Spot-On Products" document, dated 9/30/11 (Received 10/11/11), but we have also taken the opportunity in this amendment to make a few minor word and format changes. However, there have been no revisions of any efficacy claims. Also, enclosed is the Final Printed Labeling for this product, as requested in the aforementioned EPA document.

The proposed changes to the draft labeling are:

Page 1:

- Revision of the weight and age restriction statement, with a box surrounding it.
 The minimum weight was determined from the EPA-accepted Companion Animal Safety studies for this product.
- 2. Revision of the referral statements.
- 3. Addition of the "cat prohibition" icon. We do not feel this is necessary since the identical formulation is registered and sold for use on cats. We are acquiescing to the Agency on this point, but ask that this be reconsidered, as it may cause unnecessary worry by the users of the product.

Page 2:

- 4. In the "HAZARDS TO DOMESTIC ANIMALS," addition of the minimum weight for dogs and puppies.
- 5. Addition of "Side Effects" text in a box; basically the "boiler plate" language specified by the Agency in the aforementioned document, with slight product-specific modifications, based on the findings in the EPA-accepted Companion Animal Safety studies for this product, and from accident reports from cases of properly applied product.
- 6. Addition of "DO NOT USE ON CATS" warning box and icon. Again, this should not be necessary since the identical formulation is registered and sold for use on.

cats. We are acquiescing to the Agency on this point, but ask that this be reconsidered, since it may cause unnecessary worry by the users of the product. Furthermore, we are unaware of any specific data that determined the specific separation period, which we feel is not needed.

7. Addition of the 1-800 numbers for the carton.

Page 3:

 Addition of the minimum weight restriction to bullet #1 of the "HOW TO APPLY."

Page 4:

- 9. Incorporation of the required "do not allow your dog to ingest this product" statement into the language of the bullet #6 of the draft label.
- 10. Rewording of "GENERAL INFORMATION" to read "PRODUCT INFORMATION" as recommended by the Agency in reviews of other Bayer spot-on products (e.g. K9 Advantix).

Pages 5 - 9:

- No changes.

No other substantive changes have been made to this label, except for those listed above. Therefore, we hope that these minor changes to the label can be readily accepted by the Agency for this product, as well as, for the revised labels of the four other Advantage dog products — Advantage II Medium Dog, Advantage II Large Dog and Advantage II Extra Large Dog - submitted concurrently with this application. If there are any questions regarding these revisions, please contact us immediately [doug.spilker@bayer.eom; (913)-268-2751].



Via Federal Express

April 9, 2012

Document Processing Desk (AMEND- Pet Spot-on)
Office of Pesticide Programs (7505P)
U.S. Environmental Protection Agency
Room S-4900, One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202-4501

Attention: Ms. Venus Eagle/PM 01

Subject: Advantage II Medium Dog (EPA Reg. No. 11556-125)

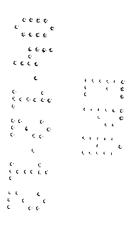
Advantage II Large Dog (EPA Reg. No. 11556-127) Advantage II Small Dog (EPA Reg. No. 11556-128) Advantage II Extra Large Dog (EPA Reg. No. 11556-128) Bayer HealthCare LLC Animat Health P.O. Box 390 Shawnee Mission, KS 6620 t-0390

Dear Ms. Eagle:

Reference is made to the current registrations of the subject products, and the Agency's letter to us, dated September 20, 2011 (received October 11, 2011), regarding "Implementation of Label Changes to Pet Spot-on Products."

Please find enclosed for the Agency's review and acceptance respective applications and revised draft labeling, dated 03/26/2012, for each of the subject dog spot-on products. Many of the revisions are in response to the aforementioned EPA "Implementation" letter, but we have also taken the opportunity in these amendments to make a few minor word and format changes. However, there have been no revisions of any efficacy claims.

The letter from the Agency requests the submission of "packaging" of these products. In addition to the enclosed "Master" labels for the products, we have also enclosed one copy of the printer's proofs of each element of the Final Printed Labeling (packaging) for these products.



Since the mandated label revisions outlined in the aforementioned Agency letter affect all pet spot-on pet registrations, we encourage the Agency to issue a PR Notice, or other regulatory document, that will also mandate a single date of packaging compliance for the entire affected industry as one. If you have any questions, please do not hesitate to call (913-268-2751).

Sincerely,

Douglas A. Spilker. Ph. D.

Manager, EPA Regulatory Affairs

Doug.Spilker@Bayer.com

Enclosures:

- 1) Advanatge II Small Dog Application w/att.
- 2) Advantage II Small Dog Draft label, dated 3/26/12 (3 copies)
- 3) Advantage II Small Dog Final printed labeling proofs (I copy)
- 4) Advanatge II Medium Dog Application w/atv.
- 5) Advantage II Medium Dog Draft label, dated 3/26/12 (3 copies)
- 6) Advantage Il Medium Dog Final printed labeling proofs (I copy)
- 7) Advanatge II Large Dog Application w/att.
- 8) Advantage II Large Dog Draft label, dated 3/26/12 (3 copies)
- 9) Advantage Il Large Dog Final printed labeling proofs (I copy)
- 10) Advanatge II Extra Large Dog Application w/att.
- 11) Advantage II Extra Large Dog Draft label, dated 3/26/12 (3 copies)
- 12) Advantage II Extra Large Dog Final printed labeling proofs (I copy)

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY WASHINGTON, D.C. 20460



OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

July 2, 2012

Dr. Douglas A. Spilker
Bayer HealthCare, LLC
Animal Health Division
P.O. Box 390
Shawnee Mission, KS 66201-0390

Subject:

Storage Stability and Corrosion Characteristics Data (Condition of Registration)

Your submission dated May 12, 2010

Products:

Advantage II Medium Dogs EPA Reg. No. 11556-125
Advantage II Large Dog EPA Reg. No. 11556-127
Advantage II Small Dog EPA Reg. No. 11556-128
Advantage Plus 100 for Dogs EPA Reg. No. 11556-130

Dear Dr. Spilker:

The study (MRID 48096401) submitted to fulfill the conditional data requirement for the products referred to above, in connection with registration under the Federal Insecticide, Fungicide, and Rodenticide Act, is acceptable. The condition of registration is considered fulfilled. Should you have any questions, please contact me at 703-308-8735 or chao.julie@epa.gov.

Sincerely,

Julie A. Chao

Insecticide-Rodenticide Branch Registration Division (7505P) Office of Pesticide Programs



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

OFFICE OF PESTICIDE PROGRAMS REGISTRATION DIVISION (7505P)

DATE OUT: June 28, 2012

SUBJECT: Storage Stability and Corrosion Study - Product Chemistry Review

FROM:

Bruce Kitchens / Shyam Mathur

Product Chemistry Team

Byrane Kuthers 6/28/12 sion (7505P) Show 6/28/12 Technical Review Branch / Registration Division (7505P)

TO:

Dani Daniel / Venus Eagle Olga Odiott / Richard Gebken Rosanna Louie / Mark Suarez Melody Banks / Richard Gebken Registration Division (7505P)

Company Name / Number: BAYER HEALTHCARE LLC / 11556

INTRODUCTION:

In support of previous applications, the company / applicant has submitted the one year Storage Stability and Corrosion Characteristics studies for the following products:

PM	Reg. No.	DP Barcode	Decision No.	MRID No.	PC Code
01	11556-125	378289	433954	480964-01	129099; 129032
01	11556-127	378284	433956	480964-01	129099; 129032
01	11556-128	378285	433952	480964-01	129099; 129032
01	11556-130	378293	433957	480964-01	129099; 129032
13	11556-131	370264	420374	478509-01	067501; 118831
13	11556-141	385157	443564	482937-01	109701; 129032; 129099
13	11556-142	385158	443565	482937-01	109701; 129032; 129099
13	11556-143	385161	443566	482937-01	109701; 129032; 129099
13	11556-144	385162	443567	482937-01	109701; 129032; 129099
01	11556-153	401047	463759	487832-01	129099
10	11556-154	401459	464140	487910-01	036007

SUMMARY OF FINDINGS:

The Technical Review Branch has performed a fast track review of the associated products and concludes all of the studies are "acceptable". No products exhibited degradation of the active ingredient(s) in the products or corrosion of the packing material were observed during the period of testing.

DATA PACKAGE BEAN SHEET

Date: 26-May-2010 Page t of 2 Decision #: 433952

DP #: (378285)

NON PRIA

Parent DP #:

Submission #: 874679

* * * Registration Information * * *

Registration: 11556-128 - ADVANTAGE II SMALL DOG Company: tt556 - BAYER HEALTHCARE LLC Risk Manager: RM 01 - Venus Eagle - (703) 308-8045 Room# PY t S-7228 Risk Manager Reviewer: Dani Daniel DDANIE03 Sent Date: t4-May-2010 Calculated Due Date: 01-Sep-2010 Edited Due Date: Type of Registration: Product Registration - Section 3 Action Desc: (570) CONDITIONAL REGISTRATION FOLLOW-UP; DATA REQUIRED; REQUIRES RD REVII Ingredients: 129099, Imidacloprid(9.1%) 129032, Pyriproxyfen(.46%) * * * Data Package Information * * * Expedite: Yes No Date Sent: 26-May-2010 Due Back: DP Ingredient: 129032, Pyriproxyfen 129099, Imidacloprid DP Title: Label Included:
Yes
No CSF Included:
Yes
No Parent DP #: 3-22-2012 Assigned To Date in Date Out Organization: RD / TRB Last Possible Science Due Date: 23-Jun 2016ben ____ Science Due Date: Reviewer Name: Sub Data Package Due Date: Contractor Name: * * * Studies Sent for Review * * * () Printed on Page 2

* * * Additional Data Package for this Decision * * *

No Additional Data Packages

* * * Data Package Instructions * * *

Chemistry: Bayer Animal Health has submitted to the Agency data to support their registration claim for stability and corrosio characterics study. Please review for data acceptability. Thank you. Dani Daniel



Bayer HealthCare LLC

Shawnee Mission, KS 66201-0390

Animal Health

P.O. Box 390

Via Federal Express - Express Saver

May 12, 2010

Document Processing Desk
Office of Pesticide Programs (7504P) – Additional Information /NonPRIA
U.S. Environmental Protection Agency
Room S-4900, One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202-4501

Attention: Ms. Venus Eagle/PM 01

Subject: Advantage II Small Dog (EPA Reg. No. 11556-128)

Advantage II Medium Dog (EPA Reg. No. 11556-125) Advantage II Large Dog (EPA Reg. No. 11556-127) Advantage II Extra Large Dog (EPA Reg. No. 11556-130)

Dear Ms. Eagle:

Reference is made to the current registrations of the subject products, formerly known as "Advantage Plus" products within the Agency's system; the primary brand names for these products were changed to the subject product names by the Agency on April 29, 2010.

Enclosed please find the required stability and corrosion characteristics study (OPPT Guidelines 830.6317 & 830.6320) to support the continued registration of the subject products. Please also note that these data also support the pending registration actions for Advantage IGR 5 (EPA File Symbol 11556-RLN), Advantage IGR 9 (11556-RLR) and Advantage 18 (11556-RLE). By submission of this study, we have met the required deadline of May 31, 2010 given to us by the Agency.

If you have any questions, please do not hesitate to call (913-268-2751).

Sincerely.

Douglas A. Spilker. Ph. D.

Manager, EPA Regulatory Affairs

Doug.Spilker.b@Bayer.com

Attachments:

1) Bayer Report No. 33827 (3 copies)

+Transmittal Document

1. Name and Address of Submitter

Bayer HealthCare LLC Animal Health Division

Box 390

Shawnee Mission, Kansas 66201-0390

Douglas A. Spilker, Ph.D.

Manager, EPA Regulatory Affairs

(913) 268-2751

2. Regulatory Action in Which this Package is Submitted

Submission of storage stability and corrosion characteristics report to support the continued registration of Advantage II products (EPA Reg. Nos. 11556-125, -127, -128, and -130)

3. <u>Transmittal Date</u>

May 12, 2010

4. <u>List of Submitted Studies</u>:

MRID No. Volume

1

48096401

 "Evaluation of Stability and Corrosion Characteristics of M880 Insecticide," OPPT 830.6317 & 830.6320, Bayer Report No. 33827, Rose, J., 22 pp.



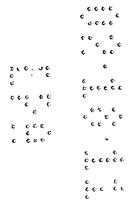
Via Federal Express 02/17/2011

Document Processing Desk (Final Printed Labeling)
Office of Pesticide Programs (7504P)
U.S. Environmental Protection Agency
Room S-4900, One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202-4501

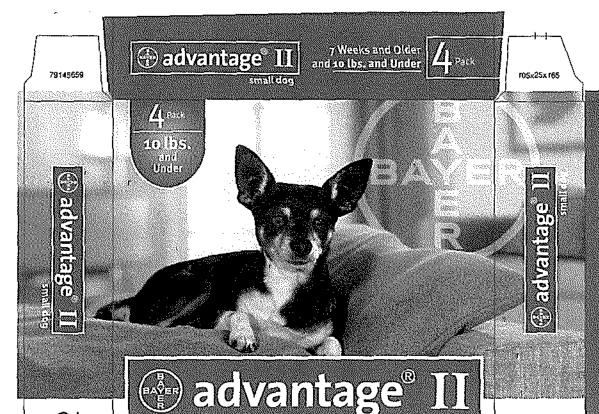
Bayer HealthCare LLC Animal Health P.O. Box 390 Shawnee Mission, KS 66201-0390

Enclosure: Application for Pesticide (other) – Final Printed Labeling (2 copies each)

Advantage II Small Dog (EPA No. 11556-128) (04461707, R.0) Advantage II Medium Dog (EPA No. 11556-125) (04461723, R.0) Advantage II Large Dog (EPA No. 11556-127) (04461725, R.0) Advantage II Extra Large Dog (EPA No. 11556-127) (04461774, R.0)



Please read Instructions o	n reverse before commet	ing form.		Form Appr	bevo	_MB No. 207	0-0060	Print Form
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		Application	for Pesti	ide - Sec	tion	l		
t. Company/Product Num 11556-128	ber			A Product Man is Eagle	edet		F	posed Classification
4. Company/Product (Nam Advantage II Small Do	ne) g		PM# 01				None Restricted	
5. Name and Address of Applicant Ilnelude ZIP Code) 8ayer HealthCare LLC, Animal Health Division P.O. Box 390 5hawnee Mission, KS 66201-0390 Check if this is a new address			6. Expedited Review. In accordance with FIFRA Section 3(c)(3) (b)(i), my product is similar or identical in composition and labeling to: EPA Reg. No. Product Name					
		<u> </u>	Section	· li				
Amendment - Expl	epones to Agency letter	dated		Final printe Agency let "Me Too" Other - Exp	ter dete Applica	tion.	t o	SEP 2 7 2010
Submission of Final Pri Contact: doug.spilker@	_	on required.	Section -	111				
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Contact Point I I I Complete items directly below for identification Name Douglas A. Spilker, Ph D.						No. (Înclude Area Code)		
Certification I certify that the stetements I have made on this form and all et I acknowledge that any knowlingly false or misleading statemen both under opplicable law.								8. Date Application Received (Stamped)
2. Signature Spall Aprille			3. Titla EPA Reg. Affairs Manager					
4. Typed Name Douglas A. Spilker, Ph D.			Date 2/	17/2011				

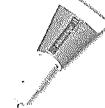


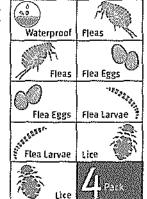
small dog

Once-a-Month Topical Treatment for Fleas and Lice On Dogs and Puppies 7 Weeks and Older and Weighing 10 lbs. and Under

- · Kills all flea life stages
- · Prevents fleas on treated dogs from infesting your home
- ations

 Treats, prevents a 	and controls lice infesta
Active ingredient	% By Welghr
Imidar toprid	
Pyrtproxyfen	0.46%
Other Ingredients	90.44%
Total	
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Waterproof



small dog

Once-a-Month Topical Treatment for Fleas and Lice

On Dogs and Pupples 7 Weeks and Older and Weighing 10 ths. and Under

READ THE ENTIRE LABEL BEFORE EACH USE

For the Prevention and Treatment of Hea and Like Infestations on Dogs

- Kills all healile stages
- Prevents fleas on treated dogs from Intesting your
- Xills fleas within 12 hours of application · Freats, prevents and controls like Intestations

PRECAUTIONARY STATEMENTS HAZARDS TO HUMANS:

Harmful if swallowed. Causes moderate eye initiation. Avoid contact with eyes or clothing. Wash hands thoroughly with soap and warm water after handling.

KAZAROSTO DOMESTIC AHIMALS

For external use only. Do not use on pupples under seven weeks of age. As with any product, consult your velering nan before using this product on debilitated, aged, pregnantor nursing animals. Individual sensitivities, while rare, may occur after using ANY pesticide product for pets, if signs prisist. or become more severe, consult a veterinarian immediately. If your animal is on mirdination, ronsult your veterinarian before using this or any other

Tor ronsumer questions rall r-800-255-6826. For medical emergencies call r-800-422-9874.

Have the product rontainer or tabel with you when calling a poison rolltrol renter or doctor, or going for treatment

f swallowed:

Call poison control center or doctor immeriately for treatment advice. Have person sip a glass of water if able to swallow, Do not Induce vomiting unless told to do so by the poison rontrol renter or doctor. Do not give anything by mouth to an unconscious person, if in eyes:

Hold eye open and rinse slowly and gently with water for 15-20 minutes.

Remove contact trases, it present after the first s minutes, then continue onsing eye. Call a poison control center or doctor for treatment

Manufactured for Bayer HeallftCare LLC. Animal Health Division, P.O. Box 390, Sitawnee Mission, KS, 66201, USA

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O 2010 Bayer Healthcare LLC

FIRST AID

If on skin: Wash with plenty of Soap and water. To Physician: Treat the patient symptomatically.

DIRECTIONS FOR USE

It is a violation of Federal Law to use this product in a manner inconsistent with its labeling.

- . Being careful not to rut close to the blister cavities, take scissors and cut off one section of the card containing a single tube.
- 2. Take the separated section, and cut into the blister cavity across the small side, close to the cap of the
- 3. Peel off the loit, and take out the tube. 4. Repeat steps 1 to 3 for each tube. HOW TO APPLY
- 1. Use only on does. Do not use on other animals. 2. Remove one applicator tube from the package. See "HOW TO OPEN" section.
- z. Hold applicator tube in an upright position. Put cap off tube.
- 4. Turn the cap around and place other end of cap back on tube.
- . Twist cap to be rak seal, then remove rap from





- 6. The dog should be standing for easy application. Part the hair on the dog's back, between the should fill the sun is visible. Place the tip of the better the style the entire skin and squeeze the twe to expense engine contents offer thy on the skin.

 De reflect his product in your cells eyes or mouth. Discardently tube as described in Storage and
- 7. Discogganger to be as described in Storage and Osposal.

 8. Under the malaconditions the product is effective for a market placever, in case of severe first investibles, silverations may be recessary earlier than followed the first re-lies at more often than once entity soften (pulsary. After first control is obtained the silveration in the retreatment schedule.



04461707. R. EPA ESI. No. 1866-184-1 EPA ESI. No. 1836-184-1







For Directions for Use, and Storage and of the Dtrposal, see supplemental labeling inside.



On Dogs and Puppies 7 Weeks and Older and Weighing 10 lbs. and Under

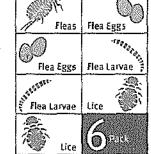
Kills all flea life stages

Prevents fleas on treated dogs from infesting your home

estations

 Treats, prevents 	and controls lice infe
Active ingredient	% By Weight
imidac loprid	9.10%
Pyrlproxylen	0.46%
Other ingredients	90.44%
Total	
Net Content: 6 Tubes, o	
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CAUHUN See back panel for First Aid. for Directions for Use, and Storage and | no n Dicposal, Seç süpplemental labeling hiside.



Fleas

68

Waterproof



Once-a-Month Topical Treatment for Fleas and Lice

On Dogs and Pupples 7 Weeks and Older and Weighing to lbs. and Undar

READ THE ENTIRE LASEL BEFORE EACH USE

For the Prevention and Treatment of Fier and Lice to festations on Dogs

- Kills affilea tile stages

- · Prevents fleas on treated dogs from infesting your
- Kits fleas victim to hours of application.
- · Treats, prevents and controls like infestitions

PRECAUTIONARY STATEMENTS HAZARDS TO HUMANS:

Harmful if swallowed. Causes moderate eye initiation. Avoid contact with eyes or clothing. Wash hands thoroughly with soap and warm water after handling.

HAZARDS TO DOMESTIC ANIMALS

For external use only. Do not use on puppies under Seven weeks of age. As with any product, consult your veterinarian before using this product on debilitated, aged, pregnant or hursing animals, individual sensitivities, while rare, may occur after using AHY pesticide product for pets. It signs persist. or become more severe, consult a veterinarian immediately, if your animal is on medication, consult your veterinarian before using this or any other

For consumer questions call c-800-a55-6826. For medical emergencies call c-800-422-9874.

FIRST AID

Have the product container or label with you when calling a poison control center or doctor, or going for

f swaKowed:

Call poison control center or doctor immediately for treatment advice. Have person sip a glass of water if able to swallow. Do not induce vomiting unless told to do so by the poison control center or doctor. Do not give anything by mouth to an unconccious person. d in eyes:

Hold eye open and rinse slowly and gently with water for SS-20 minutes.

Remove contact lenses, if present, after the first s minutes, then continue rinsing eye. Call a poison control center or doctor for treatment

Manufactured for Bayer HealthCare LLC. Animal Health Division, P.O. Box 390. Shawnee Mission, KS. 66201. USA Bayer, the Bayer Cross and Advantage are registered trademarks of Bayer. Made in Germany

O 2010 Bayer Healthcare LLC

on skin: Wash with plenty of soap and water. To Physician: Treat the patient symptomatically.

DIRECTIONS FOR USE

it is a violation of Federal Caw to use this product in a manner inconsistent with its labeling.

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- c. Being careful not to cut close to the bisseccenties, take scissors and out off one section of the card containing a single tube.
- 2. Take the separated section, and cut into the blister cavity across the small side, close to the cap of the
- 3. Peel off the fold, and take out the tube.
- 4. Repeat steps c to 3 for each tube.
- t. Use only on dogs, Do not use on other animals.
- 2. Remove one applicator tube from the package. See "HOW TO OPEN" section.
- 3. Hold applicator tube in an upright position. Pull cap off tube.
- 4. Turn the cap around and place other end of cap back on tube
- 5. Twist capto break seal, then remove cap from





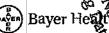
6. The day should be standing for easy application. Part the hair on the dog's back, between the shoulder blades, until the skin is visible. Place the tip of the tube on the skin and squeeze the tube to expel the entire contents directly on the skin.

Do not get this product in your pet's eves or mouth.

Discard empty tube as described in Storage and DiscosaL

Under normal conditions the product is effective Linder normal conditions the product is effective for a month, thatever, in case of servere fleat infesticing of Batheer may be necessary earlier than but waste, by notire treat more often than once every objective days. After fleat control is obtained, in control is a proportion of proportion of servery servery servers and server in servery servers and servers ar

04465715, R.O. EPA ES1. tto, 11556-0EU-c EPA Reg. No. 11556-128



Lot No.:



Once-A-Month Topical Treatment for Fleas and Lice On Dogs and Puppies 7 Weeks and Older and Weighing 10 lbs. and Under

READ THE ENTIRE LABEL BEFORE EACH USE.

For the Prevention and Treatment of Flea and Lice Infestations on Dogs

- Kills all flea life stages
- Prevents fleas on treated dogs from infesting your home
- One treatment prevents further flea infestations for a month
- Kills fleas on dogs within 12 hours of application
- Treats, prevents and controls lice infestations
- Waterproof
- Fragrance-free

'Active Ingredient	% By Weight
İmidacloprid	
Pyri proxyfen	
Other Ingredients	90.44%
Total	

KEEP OUT OF REACH OF CHILDREN DIRECTIONS FOR USE

CAUTION

See below for First Aid and Precautionary Statements.

PRECAUTIONARY STATEMENTS HAZARDS TO HUMANS: Harmful if

swallowed. Causes moderate eye irritation. Avoid contact with eyes or clothing. Wash hands thoroughly with soap and warm water after handling.

HAZARDS TO DOMESTIC ANIMALS

For external use only. Do not use on pupples under 7 weeks of age. As with any product, consult your veterinarian before using this product on debilitated, aged, pregnant or nursing animals, individual sensitivities, while rare, may occur after using ANY pesticide product for pets.

If signs parsist, or become more severe, consult a veterinarian immediately. If your animal is on medication, consult your veterinarian before using this or any other broduct.

For consumer questions call 1-800-255-6826. For medical emergencies call 1-Boo-422-9874.

FIRSTAID

Have the product container or label with you when calling a poison control center or doctor, or going for treatment.

if swallowed: Call poison control center or doctor immediately for treatment advice. Have person sip a glass of water if able to swallow. Do not induce vomiting unless told to do so by the poison control center or doctor. Do not give anything by mouth to an unconscious person.

If in eyes: Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye. Call a poison control center or doctor for treatment advice.

if on skin: Wash with plenty of soap and

To Physician: Treat the patient symptomatically.

it is a violation of Federal Law to use this product in a manner inconsistent with its labeling.

HOW TO OPEN 💍



- 1. Being careful not to cut close to the blister cavities, take scissors and cut off one section of the card containing a single tube.
- Take the separated section, and cut into the blister cavity across the small side, close to the cap of the tube.
- 3. Peel off the foil, and take out the tube.
- 4. Repeat steps 1 to 3 for each tube.

HOW TO APPLY

- 1. Use only on dogs. Do not use on other animals.
- 2. Remove one applicator tube from the package, See "HOW TO OPEN" section.
- 3. Hold applicator tube in an upright position. Pull cap off tube.







- 4. Turn the cap around and place other end of cap back on tube.
- 5. Twist cap to break seal, then remove cap from tube.





6. The dog should be standing for easy application. Part the hair on the dog's back, between the shoulder blades, until the skin is visible. Place the tip of the tube on the skin and squeeze the tube to expel the entire contents directly on the skin. Do not get this product in your pet's eyes or <u>mouth.</u>

- 7. Discard empty tube as described in Storage and Disposal.
- 8. Under normal conditions the product is effective for a month. However, in case of severe flea infestation, retreatment may be necessary earlier than four weeks. Do not re-treat more often than once every seven (7) days. After flea control is obtained, return to a monthly retreatment schedule.

ADDITIONAL INFORMATION

The successive feeding activity of fleas on dogs frequently elicits a hypersensitivity skin disorder known as flea allergy dermalitis (FAD) or flea bite hypersensitivity. Trealment of dogs with Advantage II rapidly kills fleas within 12 hours which may reduce the incidence of this condillon.

Advantage II kills existing fleas on dogs within 12 hours. Reinfesting fleas are killed wilhin 2 hours with protection against further flea infestation lasting for four (4) weeks. Preexisting pupae in the environment may continue to emerge for six (6) weeks or longer depending upon the climatic conditions.

Fleas, flea eggs, and flea larvae in the dog's environment are killed following contact with an Advantage II treated pet. Advantage II provides multi-stage flea control effectively breaking all flea life-cycle stages for quick and lasting control of flea populations.

Advantage II kills adult fleas quickly (within 12 hours), inhibits the development of immature flea life stages and prevents them from reaching the biting adult stage.

Advantage II kills chewing lice that infest dogs and puppies, and prevents further infestations.

Advantage Ilis waterproof and remains effective following a shampoo treatment, swimming or after exposure to rain or sunlight.

Monthly treatments are required for optimal control and prevention of fleas.

STORAGE AND DISPOSAL

Do not contaminate water, food or feed by storage or disposal.

Pesticide Storage: Store in a cool, dry place. Pesticide Disposal and Container Handling: Nonrefillable container.

If empty: Do not reuse or refill this container. Place in trash or offer for recycling if available. If partly filled: Call your local solid waste agency or 1-800-422-9874 for disposal instructions. Never place unused product down any indoor or outdoor drain.

LIMITED WARRANTY AND LIMITATION OF DAMAGES

8ayer HealthCare LLC, Animal Health Division warrants that this material conforms to the chemical description on the label. TO THE EXTENT CONSISTENT WITH APPLICABLE LAW, BAYER MAKES NO OTHER EXPRESS OR IMPLIED WARRANTY, INCLUDING ANY OTHER EXPRESS OR IMPLIED WARRANTY OF FITNESS OR MERCHANTABILITY, and no agent of Bayer is authorized to do so except in writing with a specific reference to this warranty. Any damages arising from a breach of this warranty shall be limited to direct damages and shall not include consequential commercial damages such as loss of profits or values, etc.

Manufactured For
Bayer HealthCare LLC, Animal Health Division,
P.O. Box 390, Shawnee Mission, Kansas 66201 USA
Bayer, the Bayer Cross and Advantage are
registered trademarks of Bayer
© 2010 Bayer HealthCare LLC
Made In Germany

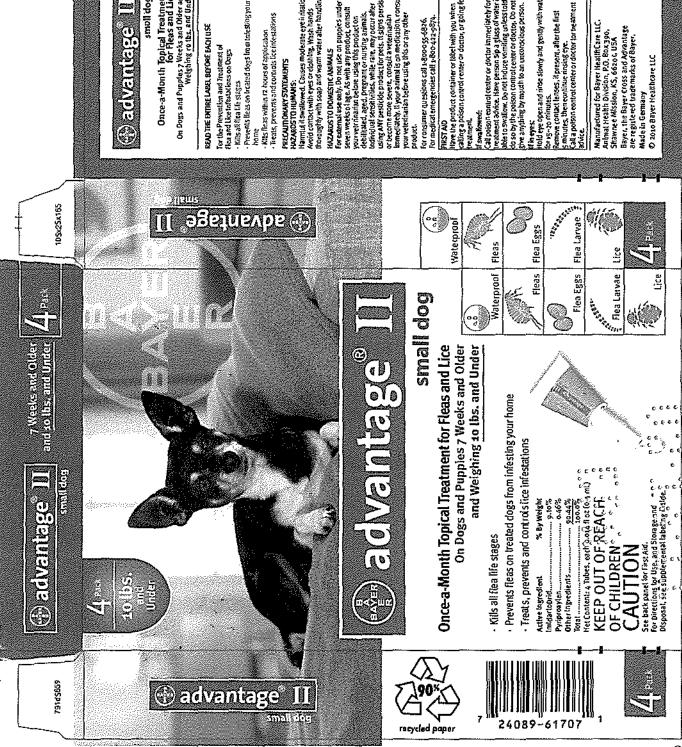
Advantage II is protected by the following U.S. patents: 6,232,328 and 6,001,858

79145896 83000539/04461707/04461715, R.O EPA Est. No. 11556-DEU-1 EPA Reg. No. 11556-128





를 돌	PM no.: 791 CR no.: 804	5404 6 240	Bayer Animal Health GmbH approved by BAH-PS-TO/PT	In case of questions phone: +49 2173 38
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% ₹ ₺	Colours: Schwarz	Operator ID AD	by	Uwe Müller (TGMUÉ)4614 Otto Wilinski (VTWIL)4701
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smoll dog

Once-a-Month Topical Treatment for Reas and Lice On Dogs and Pupples 7 Weeks and Older and Weighing to the and Under

READ THE ENTIRE LARKL BEFORE EACH USE for the Prevention and Treatment of these and Lice Infestations on Dega

Prevents liezs on incated dogs from infesting your Kitts attitua tile stages

- Kits Reas within ra hours of application - Treats, prevents and controls lice infestations

PRECAUTIONARY STATEMENTS

family it swakowed. Causes moderate eye initation, woid contact with eyes or clothing. Wash hands hornighly with soap and warm water after handling.

ecome more Severe, consult a veterinarian nedistely. Il your animal is on medication, ronsult r veterinarian before using this or any other bilitated, aged, pregnant or nursing animals. Jividual sensitivities, while rare, may occur after ing ANY pesticide product for pets, it signs persi inarian belore using this product on

ronsumer questions call 1-800-055-6826. medical emergencies call 1-800-412-9872

are the product container or label with you when sling a poison control renter or doctor, or going for

all poison control center or doctor immediately for eatment advice. Have person sip a glass of water if ble to swallow. Do not induce womling unless told to so by the poison control center or doctor. Do not amything by mouth to an unconscious person.

ye open and ninse stowty and gently with water

Manufactured for Bayer HealthCare LLC Anlmat Health Division, P.O. Box 390, Strawnee Mission, KS, 6620, USA

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To Physician: Treat the parlent symptomatically fon skin: Wash with plenty of soap and water

It is a violation of free ral Law to use this product in a manner inconsistent with its labeling.

How to open O

1. Being careful not to cus closes to the biblish readlies, lake scissors and ets of one section of the card constaining a single tube.

1. Take the scoparated section, and cut from the biblish cashing across the small side, close to the eap of the

3. Peel of the folk and take out the tube. 4. Repeat 20551 to 3 for each tube. HOW TO APPLY

1. Use only an degr. Do not use on other animats.
2. Remove one against postedige.
2. Profer To OPEM* section.
3. Hold applicator tube in an upright position.
Pull cap off tube. 4. Tum the cap around and place other end of cap back on lube.

Twist cap to break Seal, then remove cap from

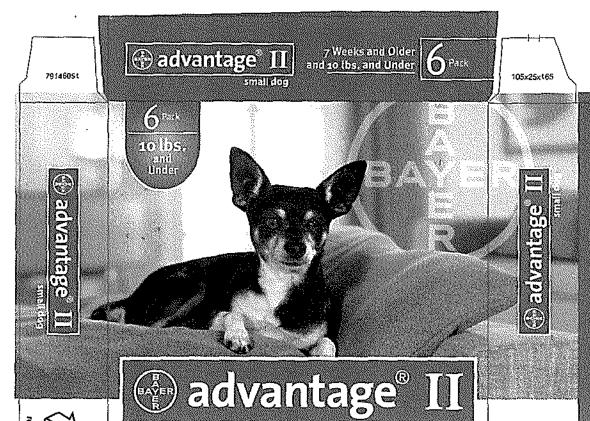
De not set his product in your pers eyes or more 7. Decard empty tabe as described in Storage and Disposal.

8. Under normal conglitors the product is effective

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Lot No.:

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small dog

Once-a-Month Topical Treatment for Fleas and Lice On Dogs and Puppies 7 Weeks and Older and Weighing 10 lbs. and Under

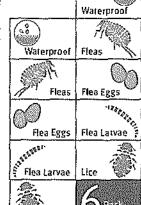
Kills all flea life stages

4089

- Prevents fleas on treated dogs from infesting your home
- Treate prevents and controls lice infestations

· neats, prevents	and tonuvols ace miesi
Active ingredient	% By Weight
tmldacloprid	9.to%
Pyriproxylen	0.46%
Other Ingredients	90.44%
Total	
Net Content: 6 Tubes, e	actro.o.a floz (q 4 mL)
KEEP OUT C)F₹₽₽AC\\
OF CHILDRE	No 5 7,2 6,50
CALITIO	M `

じんしいしい See back panel for First Aid. For Oirections for Use, and Stora ge, and in a fi Disposal, Cell Suppliented lattering inside."





Once-a-Month Topical Treatment for Fleas and Lice

On Pogs and Pupples 7 Weeks and Older and Weighing to the and Under

READ THE ENTIRE LABEL BEFORE EACH USE

Tor the Prevention and Treatment of Rea and Like infestiglions on Dogs

- Kills all flea life staged
- · Prevents fleas on treated dogs from infesting your
- Kills fless within 12 hours of application · Yizats, prevents and controls like infestations

PRECAUTIONARY STATEMENTS HAZARDS TO HUMANS:

tlarmful if swallowed. Causes moderate eye Irritation. Avoid contact with eyes or clothing. Wash hands thoroughly with soap and warm water after handling.

HAZARDS TO ODMESTIC ARRMALS

For external use only. Do not use on puppies under seven weeks of age, As with any product, consult your veterinarian before using this product on debilitated, aged, pregnant or nursing animals. Individual sensitivities, while rare, may occur after using AVY pesticide product for pets. If cigns persist, or become more severe, consult a veterinarian immediately. If your animal is on medication, consult your veterinarian before using this or any other

For concumer questions call c-800-255-6826. 7or medical emergencies call r-800-422-9874.

Have the product container or label with you when calling a poison control center or doctor, or going for

f swakowed:

C20 poison consolicenter or doctor larmediately for creatment advice. Have person sip a glacs of water if able to swallow. Do not induce vomiting unless told to do so by the poison control center or doctor. Do not give anything by mouth to an unconccious person.

tiin eyes: Hold eye open and rinse slowly and gently with water for rs-20 minutes.

Remove contact lenses, if present, after the first s minutes, then continue rinsing eye. Call a poison control centecor doctor for treatment

Manufactured for Bayer HealthCare tLC. Animal Health Oivision, P.O. Box 390, Shawnee Mission, KS, 6620c, USA Bayer, the Bayer Cross and Advantage

are registered trademarks of Savec Made in Germany

O 2010 Sayer Healthcare LLC

If on skin: Wash with plenty of soap and water. To Physician: Treat the patient symptomatically.

DIRECTIONS FOR USE

It is a violation of Federal Lawto use this product in a manner inconsistent with its labeling.

- HOW TO OPEN S take scissors and cut off one section of the card containing a single tube.
- Take the separated section, and est into the bister carring across the small side, close to the cap of the
- 3. Peel off the foil, and take out the tube. 4. Repeat steps 5 to 3 for each tube.
- HOW TO APPLY c. Use only on dogs. Do not use on other animals. Remove one applicator tube from the package,
- See "HOW TO OPEN" Section. 3. Hold applicator tube In an upright position.
- Pull cap off tube. 4. Turn the cap around and place other end of cap
- back on tube. 5. Twist capto break seal, then remove cap from

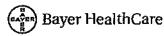




- The dog should be standing for easy application. Part the hair on the dog's back, between the shoulder blades, until the Skin is visible, Place the tip of the tube on the skin and squeeze the tube to expel the entire contents directly on the skin.
- Do not set this product in your pel's eves or mouth.

 Discard empty tube as described in Storage and
- 8. Under normal conditions the product is effective for a month, However, in case of severe flea Infestation, retreatment may be necessary earlier than four weeks. Do not re-treat more often than once every seven (y) days. After thes control is obtained, return to a monthly retreatment

0446C715. R.o EPA Est. No. cc556-0EU-1 EPA Reg. No. c1556-128



Lot No.:



small dog

Once-A-Month Topical Treatment for Fleas and Lice On Dogs and Puppies 7 Weeks and Older and Weighing 10 lbs. and Under

READ THE ENTIRE LABEL BEFORE EACH USE.

For the Prevention and Treatment of Flea and Lice Infestations on Dogs

- · Kills all Ilea life stages
- Prevents fleas on treated dogs from infesting your home
- · One treatment prevents further flea infestations for a month
- Kills fleas on dogs within 12 hours of application
- · Treats, prevents and controls lice injestations
- Waterproof
- Fragrance-free

Active ingredient	% By Weight
imidacloprid	9.10%
Pyriproxyfen	
Other Ingredients	90.44%
Total	100.0%

KEEP OUT OF REACH OF CHILDREN

CAUTION

See below for First Aid and Precautionary Statements.

PRECAUTIONARY STATEMENTS

HAZARDS TO HUMANS: Harmful if swallowed. Causes moderate eye irritation. Avoid contact with eyes or clothing. Wash hands thoroughly with soap and warm water after handling.

HAZARDS TO DOMESTIC ANIMALS

for external use only. Do not use on puppies under 7 weeks of age. As with any product, consult your veierinarian before using this product on debilitated, aged, pregnant or nursing animals. Individual sensitivities, while rare, may occur after using ANY pesticide product for pets.

if signs persist, or become more severe, consult a veterinarian immediately. If your animal is on medication, consult your veterinarian before using this or any other product.

For consumer questions call 1-800-255-6826. For medical emergencies call 1-800-422-9874.

FIRST AID

Have the product container or label with you when calling a poison control center or doctor, or going for treatment.

If swallowed: Call poison control center or doctor immediately for treatment advice. Have person sip a glass of water if able to swallow. Do not induce vomiting unless told to do so by the poison control center or doctor. Do not give anything by mouth to an unconscious person.

If In eyes: Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye. Call a poison control center or doctor for treatment advice.

If on skin: Wash with plenty of soap and

To Physician: Treat the patient symptomatically.

DIRECTIONS FOR USE

it is a violation of Federal Law to use this product in a manner inconsistent with its labeling.

HOW TO OPEN &

- Being careful not to cut close to the blisier cavitles, take scissors and cut off one section of the card containing a single tube.
- 2. Take the separated section, and cut into the blister cavity across the small side, close to the cap of the tube.
- 3. Peel off the foll, and take out the tube.
- 4. Repeat steps 1 to 3 for each tube.

HOW TO APPLY

- Use only on dogs. Do not use on other animals.
- Remove one applicator tube from the package, See "HDW TO DPEN" section.
- Hold applicator tube in an upright position.
 Pull cap off tube.







- 4. Turn the cap around and place other end of cap back on tube.
- Twist cap to break seal, then remove cap from tube.





6. The dog should be standing for easy application. Part the hair on the dog's back, between the shoulder blades, until the skin is visible. Place the tip of the tube on the skin and squeeze the tube to expel the entire contents directly on the skin.

Do not get this product in your pet's eves or mouth.

- 7. Discard empty tube as described in Storage and Disposal.
- 8. Under normal conditions the product is effective for a month. However, in case of severe flea infestation, retreatment may be necessary earlier than four weeks. Do not re-treat more often than once every seven (7) days. After flea control is obtained, return to a monthly retreatment schedule.

ADDITIONAL INFORMATION

The successive feeding activity of fleas on dogs frequently elicits a hypersensitivity skin disorder known as flea altergy dermatitis (FAD) or flea bite hypersensitivity. Treatment of dogs with Advantage II rapidly kills fleas withfi 12 hours which may reduce the incidence of this condition.

Advantage if kills existing fleas on dogs within 12 hours. Reinfesting fleas are killed within 2 hours with protection against further flea intestation lasting for four (4) weeks. Preexisting pupae in the environment may continue to emerge for six (6) weeks or longer depending upon the climatic conditions.

Fleas, flea eggs, and flea larvae in the dog's environment are killed following contact with an Advantage II treated pet. Advantage II provides multi-stage flea control effectively breaking all flea life-cycle stages for quick and lasting control of flea populations.

Advantage II kills adult fleas quickly (within 12 hours), inhibits the development of immature flea life stages and prevents them from reaching the biling adult stage.

Advantage II kills chewing lice that infest dogs and puppies, and prevents further infestations.

Advantage It is waterproof and remains effective following a shampoo treatment, swimming or after exposure to rain or sunlight.

Monthly treatments are required for optimal control and prevention of fleas.

STORAGE AND DISPOSAL

Do not contaminate water, food or feed by storage or disposal.

Pesticide Storage: Store in a cool, dry place. Pesticide Disposal and Container Handling: Nonrefillable container.

If empty: Do not reuse or refill this container. Place in trash or offer for recycling if available. If partty filled: Call your local solid waste agency or 1-800-422-9874 for disposal instructions. Never place unused product down any indoor or outdoor drain.

LIMITED WARRANTY AND LIMITATION OF DAMAGES

Bayer HealthCare LLC, Animal Health Division warrants that this material conforms to the chemical description on the label. TO THE EXTENT CONSISTENT WITH APPLICABLE LAW, BAYER MAKES NO OTHER EXPRESS OR IMPLIED WARRANTY, INCLUDING ANY OTHER EXPRESS OR IMPLIED WARRANTY OF FITNESS OR MERCHANTABILITY, and no agent of 8ayer is authorized to do so except in writing with a specific reference to this warranty. Any damages arising from a breach of this warranty shall be limited to direct damages and shall not include consequential commercial damages such as loss of profits or values, etc.

Manufactured For Bayer HealthCare LLC, Animal Health Division, P.D. Box 390, Shawnee Mission, Kansas 66201 USA Bayer, the Bayer Cross and Advantage are registered trademarks of Bayer © 2010 Bayer HealthCare LLC Made in Germany

Advantage II is protected by the following U.S. patents: 6,232,328 and 6,001,858

79145896 83000539/04461707/04461715, R.O EPA Est. No. 11556-DEU-1 EPA Reg. No. 11556-128





	PM no.: 79154046 CR no.: 004240		Bayer Animal Health GmbH approved by BAH-PS-TO/PT	In case of questions phone; +49 2173 38
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June 01, 2011

Document Processing Desk Office of Pesticide Programs (7504P) – NonPRIA U.S. Environmental Protection Agency Room S-4900, One Potomac Yard 2777 South Crystal Drive Arlington, VA 22202-4501

Attention: Ms. Venus Eagle/PM01

Subject: Advantage II Kitten (EPA Reg. No. 11556-150)

Advantage II Small Cat (EPA Reg. No. 11556-151)
Advantage II Large Cat (EPA Reg. No. 11556-152)
Advantage II Small Dog (EPA Reg. No. 11556-128)
Advantage II Medium Dog (EPA Reg. No. 11556-125)
Advantage II Large Dog (EPA Reg. No. 11556-127)

Advantage II Extra Large Dog (EPA Reg. No. 11556-130)

Bayer HealthCare LLC Animal Health P.O. Box 390 Shawnee Mission, KS 6620 t

Bayer HealthCare LLC, Animal Health Division received notice from the Agency for the conditional registration requirement of enhanced quarterly incident reporting for Advantage II Dog and Cat registrations on April 29, 2010 and June 24, 2010 respectively. This enhanced reporting was to begin with the quarter starting January 01, 2011. In compliance with this request, Bayer is providing the following listing of incident reports along with tables of additional analysis as requested in the Agency's letters of April 29, 2010 and June 24, 2010. In addition, Bayer's letters to the Agency regarding notification of first shipment dated December 09, 2010 are attached for reference.

This submission includes the following tables covering incident reporting from January 01, 2011 through March 31, 2011:

Summary Table (multiple pages due to length)
Breed Summary
Age Range Summary
Clinical Signs Summary
Organ System Summary
Patient Weight Range Summary
Product Weight Range Summary



Page 2 of 3

Route of Exposure Summary Secondary Exposure Summary

Due to the length of some of the tables and to provide the Agency the ability to sort, this data is being provided electronically on a CD. The data was extracted from Bayer's pharmacovigilance data base (P.V. Works).

Deaths

Deaths were reported in two (2) felines that had previously received treatment with Advantage II during the period of review. Specifics are as follows:

Animal Health P.O. Box 390 Shawnee Mission, KS 66201

Bayer HealthCare LLC

2011-US0006708

An unspecified Advantage II product (unknown if for Dogs or Cats and unknown dose) was applied to a 6 year old male cat of unknown weight and breed. An undetermined time post-application, the cat made a low, grumbling sound, his body went limp, and he wasn't moving. The owner took the cat to a veterinarian who was unable to resuscitate the cat. No necropsy examination was performed.

Assessment:

Death would not be expected with topical use of the product. With no necropsy being performed it is impossible to verify cause of death and any involvement the product may have had. The product was applied to other cats in the household at the same time without consequence. The attending veterinarian suspects cardiac arrest of unknown reason and the veterinarian did not believe the event was product-related.

2011-US0007111

On 25 Mar 2011 Advantage II Large Cat was applied to Corduroy an 11 pound, 10 year old, neutered male, Domestic Shorthair per labeled directions. At the same time Advantage II was applied a Capstar was given per the direction of the vet. Capstar and Advantage II were administered to Corduroy due to a massive flea infestation that was causing severe anemia. At an unspecified time after application Corduroy became anorexic, wouldn't drink, was lethargic and ended up passing away on 27 Mar 2011. Assessment:



Page 3 of 3

Symptoms leading to death would not be expected with the topically acting product. The patient also had severe anemia which needs to be considered. With out a necropsy being performed it is impossible to verify the cause of death and any involvement the product may have had. What role, if any, the concomitant medications played in this case cannot be determined as well. The owner noted she did not believe that the product played a role in the patient's death.

We believe this summary of data meets the requested information in the Agency's requirements for enhanced reporting as outlined in its January 19, 2011 communication to Bayer.

A report with the confidential sales information and additional analysis of incident rates based on doses sold is being sent to the Registration Division, Immediate Office (attn. Ms. Kimberly Nesci).

If there are any questions regarding this submission, please contact me by phone at 913.268.2573 or by e-mail at gary.brumley@bayer.com.

Bayer HealthCare LLC Animal Health P.O. Box 390 Shawnee Mission, KS 66201

Gary Brumley Senior Consultant Regulatory Affairs



Via Federal Express - Express Saver

December 9, 2010

Document Processing Desk Office of Pesticide Programs (7504P) - NonPRIA U.S. Environmental Protection Agency Room S-4900, One Potomac Yard 2777 South Crystal Drive Arlington, VA 22202-4501

Attention:

Ms. Venus Eagle/PM 01

Subject:

- Advantage II Small Dog (EPA Reg. No. 11556-128) = Advantage II Medium Dog (EPA Reg. No. 11556-125)... Advantage II Large Dog (EPA Reg. No. 11556-127) -

Advantage II Extra Large Dog (EPA Reg. No. 11556-130)

Animal Health P.O. Box 390

Bayer HealthCare LLC

Shawnee Mission, KS 66201-0390

Dear Ms. Eagle:

Reference is made to the current registrations of the subject products. One of the conditions of acceptance of the subject registrations is that "[We] must provide the Agency with a projected release for shipment at least 30 days in advance."

Therefore, we are hereby notifying the Agency that our first anticipated shipment of product will be on or after January 17, 2011.

If you have any questions, please do not hesitate to call (913-268-2751).

Sincerely,

Douglas A. Spilker, Ph. D.

Manager, EPA Regulatory Affairs

Doug.Spilker@Bayer.com

Cc: K. Davis (EPA) - email

107

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY WASHINGTON, D.C. 20460



OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

JUN 22 2010

Douglas Spilker, Ph.D Bayer HealthCare LLC, Animal Health Division P.O. Box 390 Shawnee Mission, KS 66201-0390

Dear Dr. Spilker:

Subject:

Revised Basic Confidential Statements of Formulation (CSFs)

Advantage II Small Dog, EPA Reg No. 11556-128 Advantage II Medium Dog, EPA Reg No. 11556-125 Advantage II Large Dog, EPA Reg No. 11556-127 Advantage II Extra Large Dog, EPA Reg No. 11556-130

Your submission dated June 1, 2010

The CSFs referred to above, submitted in connection with your application for registration under the Federal Insecticide, Fungicide, and Rodenticide Act, as amended are acceptable. All previously dated Basic CSFs for this product are superseded and are considered obsolete.

If you have any questions, please contact Autumn Metzger at (703) 305-5314 or metzger.autumn@epa.gov.

 \mathcal{M} .

Regards.

Venus Eagle (PM 01)

Insecticide-Rodenticide Branch Registration Division (7505P) FAST-TRACK AMENIMENTS—Completeness Screening Checklist
Experts In-Processing Signature:

Exp	erts In-Processing Signature:	4	M-1	
EPA	Reg. Number: 1/555-128 EPA Receipt Date: 6/z,			
	Check List item		No	NA
1	Application Form (EPA Form 8570-1)—signed?	V		
	C. E. C.			
	Confidential Statement of Formula (EPA Form 8570-29) – signed?			
3	Certification with Respect to Citation of Data (EPA Form 8570-34) signed?			W
4	Formulator's Exemption Statement (EPA Form 8570-27) - signed?			V
5	Data Matrix (EPA Form 8570-35) [Applicable, for adding me-too uses] a) Selective Method? b) Cite-All Method? Applicant owns data or list only the companies offered to pay c) Public copy of Matrix provided? See PR Notice 98-5			
6	Is Label Included? (5 copies)			
·	Comments: NON FOOD			
	I neils appores.			



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY WASHINGTON, D.C. 20460

June 3, 2010

OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

DOUGLAS A. SPILKER, PH.D. BAYER HEALTHCARE LLC ANIMAL HEALTH DIVISION PO Box 390 SHAWNEE MISSION, KS 66201-0390

PRODUCT NAME: ADVANTAGE II SMALL DOG COMPANY NAME: BAYER HEALTHCARE LLC

OPP IDENTIFICATION NUMBER: EPA FILE SYMBOL: 11556-128 EPA RECEIPT DATE: 06/02/10

SUBJECT: RECEIPT OF AMENDMENT

DEAR REGISTRANT:

The Office of Pesticide Programs has received your application for an amendment and it has passed an administrative screen for completeness.

During the initial screen we determined that the application appears to qualify for fast track review. The package will now be forwarded to the Product Manager for review to determine its acceptability for fast track status.

If you have any questions, please contact Registration Division, Risk Management Team 1, at (703) 308-8045.

Sincerely,

P. h. Moone Front End Processing Staff

Information Services Branch

Information Technology & Resources Management Division

Fee for Service

{875707?~

This package includes the following	for Division
○ New Registration	O A D
Amendment	│
□ Studies? □ Fee Waiver?	
□ volpay % Reduction:	Risk Mgr. 1
Receipt No. S-	875707
EPA File Symbol/Reg. No.	11556-128
Pin-Punch Date:	6/2/2010
This item is NOT subject t	o FFS action.
Action Code:	Parent/Child Decisions:
Requested: Granted:	MN-PEE
Amount Due: \$	TO A STATE OF THE
Dresto approved. S. Rock 6/8/10	
Inert Cleared for Intended Use	Uncleared Inert in Product
Reviewer: DVM (Att	Date: 6/3/10
Remarks:	

Inert ingredient information may be entitled to confidential treatment **Print Form** Please read instructions on reverse before completing form. Farm Approved. OMB No. 2070-0060 Approval expires 2-28-**OPP Identifier Number** Registration United States **Environmental Protection Agency Amendment** Washington, DC 20460 Other Application for Pesticide - Section I 1. Compeny/Product Number 2. EPA Product Menager 3. Proposed Classification 11556-128 V. Eagle X None Restricted 4. Company/Product (Name) PM# Advantage II Small Dog Team 01 5. Nome and Address of Applicant (Include ZIP Code) 6. Expedited Reveiw. In accordance with FIFRA Section 3[c][3] Bayer HealthCare LLC, Animal Health Division (b)(i), my product is similar or identical in composition and labeling P. O. Box 390 EPA Reg. No. Shawnee Mission, KS 66201-0390 Check if this is a new address **Product Name** Section - II Final printed labels in repeanse to Amendment - Explain below. Agency letter dated "Me Too" Application. Resubmission in response to Agency letter dated. Notification - Explain below. Other - Explain below. Explanation: Use additional page(s) if necessary. (For section I and Section II.) Enclosed for Agency acceptance are 2 copies of the Confidential Statement of Formula, dated 06/01/10, revised to widen the certified , and update other information. Please see attached for further information. Minor formulation change (no data to review); Non-PRIA action. Section - III 1. Meterial This Product Will Be Packaged in: Unit Pockaging Water Saluble Packeging 2. Type of Container Child-Resistant Peckeging Meta! Yes Yes Yes Plastic Next Νo No Gless Pepar If "Yes" If "Yes" No. per No. per Certification must Package wgt Other ISpecifyl Unit Packaging wgt. container container be submitted 5. Location of Label Directions 3. Location of Nat Contents Information 4. Size(sl Ratail Container On Label On Labeling accompaning product Contoiner 5. Manner in Which Lebel is Affixed to Product Lithograph Other Paper glued Stonciled Section - IV 1. Contact Point (Complete items directly below for identification of individual to be contacted, if necessary, to process this application.) Title Telephone No. (Înclude Atea Code) Name Douglas A. Spilker, Ph. D. (doug.spilker.b@bayer.com) Manager, EPA Regulatory Affairs 9:3-268-2751 8. Date Application Certification ୍ Raceived I certify that the statements I have made on this form and all attachments thereto are true, accurate and complete. i acknowledge that any knowlingly felse or misleading statement may be punishable by fine or imprisonment or (Stamped) both under applicable law. 3. Title 2. Signature . Julle Manager, EPA Regulatory Affairs 5. Date 4. Typed Neme 01 June 2010 Douglas A. Spilker, Ph. D.



Bayer HealthCare LLC

Shawnee Mission, KS 66201-0390

Animal Health P.O. Box 390

Via Federal Express

June 1, 2010

Office of Pesticide Programs (7504P) – Amendments/NonPRIA U.S. Environmental Protection Agency Room S-4900, One Potomac Yard 2777 South Crystal Drive Arlington, VA 22202-4501

Attention:

Ms. Venus Eagle/PM 01

Subject:

Advantage II Small Dog (EPA Reg. No. 11556-128) Advantage II Medium Dog (EPA Reg. No. 11556-125) Advantage II Large Dog (EPA Reg. No. 11556-127)

Advantage II Extra Large Dog (EPA Reg. No. 11556-130)

Dear Ms. Eagle:

Enclosed please find applications for the revision of the Confidential Statements of Formula for the subject products. All of the revisions are identical for all four products, so we would appreciate it if all four actions be assigned to the same reviewer. Although these are amendments, there are no data to review, and we hope that these could be expedited during the review and acceptance process.

If you have any questions, please do not hesitate to call (913-268-2751).

Sincerely,

Douglas A. Spilker. Ph. D.

Manager, EPA Regulatory Affairs

Doug.Spilker.b@Bayer.com

Enclosures: 4 Applications for Amendment, dated 06/01/10

Via Federal Express



June 1, 2010

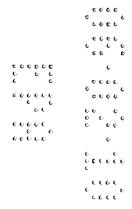
Document Processing Desk (Amend - Non-PRIA Action) Office of Pesticide Programs (7504P) U.S. Environmental Protection Agency Room S-4900, One Potomac Yard 2777 South Crystal Drive Arlington, VA 22202-4501

Attention: Ms. Venus Eagle, PM Team 01 Registration Division

Advantage II Small Dog (EPA Reg. 11556-128)

- a. Form 8570-1 Application for Amendment
- b. Attachment to Application (1 page)
- c. Confidential Statement of Formula, dated 06/01/10 (2 copies)
- d. Confidential Statement of Formula, dated 09/09/09 (Supersedes) w/EPA Acceptance letter, dated 11/04/09

Bayer HealthCare LLC Animal Health P.O. Box 390 Shawnee Mission, KS 66201-0390





Material to be added to an e-Jacket/Jacket

Re	g. No. <u>/1SS6-128</u> Decision # <u>440 180</u>
De	escription: Ampled Mynatia
	• ·
1.	Placement within the e-Jacket/jacket:
	Default: (chronological, top = newest)
	☐ File Location: (eg. "before page 45 in .pdf")
	-
2.	Send to Data Extraction contractors this material:
	☐ Newly stamped accepted label
	Notification
	□ New CSF
	☐ Other:
3.	Attach this coversheet to the top of the material or jacket. It must be well organized and clipped together, NOT STAPLED. Then give the material with this coversheet to staff in the Information Services Center (Room S-4900).
	Reviewer: Jennifer Orbanski Division: RD
	Phone: 702-347-0156 Date: 9/27/10



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY WASHINGTON, D.C. 20460

OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

SEP 2 7 2010

Mary McKinney Hunt Bayer HealthCare LLC Animal Health Division PO Box 390 Shawnee Mission, KS 66201

Subject: Notification of the addition of the agency required changes (letter dated 4/29/2010) and the optional text [Sample-not for (re)sale] for Advantage II Small Dog (EPA Reg. # 11556-128)

Dear Ms. McKinney Hunt:

The Agency is in receipt of your Application for Pesticide Notification under Pesticide Registration Notice (PRN) 98-10 dated 9/15/2010 for the product Advantage II Small Dog (EPA Reg. # 11556-128). The Registration Division (RD) has conducted a review of this request for its applicability under PRN 98-10 and finds that the action(s) requested fall within the scope of PRN 98-10. The Confidential Statement of Formula (CSF) and/or label submitted with the application has (have) been stamped "Notification" and will be placed in our records.

If you have any questions, please call me directly at 703-347-0156 or urbanski.jennifer@epa.gov.

Sincerely,

Jennifer Urbanski

Registration Division (7505P) Office of Pesticide Programs

Please read instructions on reverse b	elore complélorm			<u> </u>	orm Approved, OMB No. 2070-0060
O EDA	es	☐ Regist	ration	OPP Identifier Number	
😝 EPA 🛭 🛭	nvironmental Prote	ction Agency	☐ Amend	lment	
	Washington, DC	20460	Other:		
Application for Pesticide - Section I					
1. Company/Product Number 2. EPA Product Manager 3. Proposed Classification					
11556-128			Venus Eagle		
Company/Product (Name) Advantage II Small Dog	PM# 01/Tean	n i	None Restricted		
Name and Address of Applicant		6. Expedited Review. In accordance with FIFRA Section 3(c)(3)			
Bayer HealthCare LLC, A	on (b)(l), m	(b)(i), my product is similar or identical in composition and labeling			
PO Box 390	to:	to: EPA Reg. No			
Shawnee Mission, KS 662		Li Ariog. No.			
Check if this is a new	Product	Product Name			
Section - II					
Amendment Explain below					Agency letter dated
Resubmission in response to	*************************************				
Notification - Explain below. Explanation: Use addition	ırv (For Section	Other - Explain below or Section I and Section II.) NOTIFICATION			
Explanation: Use additional page(s) if necessary. (For Section I and Section II.) NOTIFICATION					
NON PRIA ACTION. Please see attached for more detail. SEP 2 7 2010					
Enclosed for Agency acceptance is a draft tabet for Advantage II Small Dog (EPA Reg. No. 11556-128). The proposed revisions are in					
accordance with Agency letter dated 4/29/2010 and added the optional text: (Sample-not for (re)sate].					
Section - III					
t. Material This Product Will Be i					
Child-Resistant Packaging Yes*	Unit Packaging Yes		Water Soluble Pac	Type of Container Metal	
No.	⊟ No		□ No		Plastic
	If "Yes"	No. per	ff "Yes"	No. per	Glass
*Certification must	Unit Packaging wgt	t. container	Package wgt.	conlainer	Paper
be submitted		·····			Other (Specifiy)
3. Location of Net Contents Information 4. Size(s) Retail Container 5. Location of Label Directions Container On Labet					
Label C			On Labe		
6. Manner in Which Label is Allix	ed to Product Lil	thograph	Other	On label	ing accompanying product
☐ Paper glued					
Stenciled Section - IV					
t. Contact Point (Complete items directly below for identification of individual to be contacted, if necessary, to process this application) to					
Name Title Telephone No. (Include Area					
Mary M. Hunt	Pesti	cide Registrations Ma	nager Į,	Code) \$ 255 6 913-268-2311	
Certification 6. Date Application					
I certify that the statements I have made on this form and all attachments thereto are true, accurate and complete, 1/2 Received					
acknowledge that any knowingly false or misleading statement may be punishable by fine or imprisonment or both (Stamped) under applicable law.					
2. Signature	3. Titte				
May m Hu	Pestic	Pesticide Registrations Manager			
4. Typed Name ^t	5. Date			- CCC6.	
Mary M. Hunt		1 9	-15-201	(4, 6, 6 2	

Bayer Health Care, Animal Health Division Advantage II Small Dog EPA Reg. No. 11556-128 September 15, 2010

Section II Explanation

Enclosed for Agency acceptance is a draft label for Advantage II Small Dog, EPA Reg. No. 11556-128.

The proposed revisions were made in accordance with Agency letter dated 4/29/2010, and added optional text: [Sample-not for (re)sale]

This notification is consistent with the provisions of PR Notice 98-10 and EPA regulations at 40 CFR 152.46 and no other changes have been made to the labeling or the confidential statement of formula of this product. Bayer understands that it is a violation of 18 U.S.C. Sec. 1001 to willfully make any false statement to EPA. Bayer further understands that if this notification is not consistent with the terms of PR Notice 98-10 and 40 CFR 152.46, this product may be in violation of FIFRA and Bayer may be subject to enforcement action and penalties under sections 12 and 14 of FIFRA.



Mon PRIA Action

Bayer HealthCare Animal Health



September 15, 2010

Document Processing Desk (NOTIF)
Office of Pesticide Programs (7504P)
U.S. Environmental Protection Agency
Room S-4900, One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202-4501

Attention:

Ms. Venus Eagle, Team 1

SUBJECT:

Notification of Label Revision to

Advantage II Small Dog, EPA Reg. No. 11556-128 Advantage II Medium Dog, EPA Reg. No. 11556-125 Advantage II Large Dog, EPA Reg. No. 11556-127 Advantage II Extra Large Dog, EPA Reg. No. 11556-130

Dear Ms. Eagle:

Bayer HealthCare LLC Animal Health P.O. Box 390 Shawnee Mission, KS 66201-0390

Please find enclosed for the Agency's review and acceptance, a Notification (EPA Form 8570-1 and attachment) and draft label dated September 15, 2010 for each subject product.

The proposed revisions are the required changes in accordance with Agency letter dated 4/29/2010, and the addition of optional text, [Sample-not for (re)sale], to all package sizes (SKUs).

Thank you for your assistance with this notification process, and please contact me at 913-268-2311 or <u>mary.hunt.b@bayer.com</u> if you have any questions or need further information.

Respectfully,

BAYER HEALTHCARE LLC ANIMAL HEALTH DIVISION

May Mckenney Hat

Mary McKinney Hunt

Pesticides Regulatory Manager

Encl: (4) 8570-1 Application for Pesticide Notification

(4) Attachment to Application for Pesticide Notification

(4) Draft Label (3 cc each)

(4) Highlighted Label (1 cc each)

Reason To Issue: Revised per EPA letter 4/29/10, and added optional text: [Sample – Not for Re)Sale] Supersedes: 04/28/10

NOTE TO REVIEWER: [(Brackets and parentheses indicate alternate language)]

Advantage® II Small Dog

Once-A-Month Topical Treatment for Fleas and Lice On Dogs and Puppies 7 Weeks and Older and Weighing 10 lbs. and Under

READ ENTIRE LABEL BEFORE EACH USE

For the Prevention and Treatment of Flea and Lice Infestations [on Dogs]

[Selected optional claims bulleted here from page 6 and/or 7]

•	NOTIFICATION
•	SEP 2 7 2010

•

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Active Ingredients	% By Weight
Imidacloprid	9.10%
Pyriproxyfen	0.46%
Other Ingredients	90.44%
Total	100.00%

EPA Reg. No. 11556-128

EPA Est. 11556-DEU-1

KEEP OUT OF REACH OF CHILDREN

CAUTION

[See back panel for First Aid]

[For Directions For Use, and Storage and Disposal (instructions), See supplemental labeling inside] Reason To Issue: Revised per EPA letter 4/29/10, and added Date: 09/15/2010

optional text: [Sample - Not for Re)Sale] Supersedes: 04/28/10

PRECAUTIONARY STATEMENTS

HAZARDS TO HUMANS

Harmful if swallowed. Causes moderate eye irritation. Avoid contact with eyes or clothing. Wash hands thoroughly with soap and warm water after handling.

HAZARDS TO DOMESTIC ANIMALS

For external use only. Do not use on puppies under 7 weeks of age. As with any product, consult your veterinarian before using this product on debilitated, aged, pregnant or nursing animals. Individual sensitivities, while rare, may occur after using ANY pesticide product for pets. If signs persist, or become more severe, consult a veterinarian immediately. If your animal is on medication, consult your veterinarian before using this or any other product.

	FIRST AID						
If Swallowed:	 Call a poison control center or doctor immediately for treatment advice. 						
	Have person sip a glass of water if able to swallow.						
	 Do not induce vomiting unless told to do so by the poison control center or doctor. 						
	Do not give anything to an unconscious person.						
If In Eyes: • Hold eye open and rinse slowly and gently with water for 15- 20 minutes. Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye.							
	Call a poison control center or doctor for treatment advice.						
If On Skin • Wash with plenty of soap and water.							
	HOT LINE NUMBER						
	ntainer or label with you when calling a poison control center or doctor, at. For medical emergencies call 1-800-422-9874. For consumer 255-6826.						
	NOTE TO PHYSICIAN						
Treat the patient sym	ptomatically.						

DIRECTIONS FOR USE

It is a violation of Federal Law to use this product in a manner inconsistent with its labeling

Reason To Issue:

Revised per EPA letter 4/29/10, and added

optional text: [Sample - Not for Re)Sale] S

Date: 09/15/2010 Supersedes: 04/28/10

HOW TO OPEN

- 1. Being careful not to cut close to the blister cavities, take scissors and cut off one section of the card containing a single tube.
- 2. Take the separated section, and cut into the blister cavity across the small side, close to the cap of the tube.
- 3. Peel off the foil, and take out the tube.
- 4. Repeat steps 1 to 3 for each tube.



HOW TO APPLY

- 1. Use only on dogs. Do not use on other animals.
- 2. Remove one applicator tube from the package. See "HOW TO OPEN" section.
- 3. Hold applicator tube in an upright position. Pull cap off tube.

[Visuals Depicting How to Open Applicator Tube]

- 4. Turn the cap around and place other end of cap back on tube.
- 5. Twist cap to break seal, then remove cap from tube.

[Visuals Depicting Application To Animal]

- 6. The dog should be standing for easy application. Part the hair on the dog's back, between the shoulder blades, until the skin is visible. Place the tip of the tube on the skin and squeeze the tube to expel the entire contents directly on the skin. Do not get this product in your pet's eyes or mouth.
- 7. Discard empty tube as described in the Storage and Disposal section.

Reason To Issue: Revised per EPA letter 4/29/10, and added Opate: 09/15/2010 optional text: [Sample – Not for Re)Sale] Supersedes: 04/28/10

8. Under normal conditions the product is effective for a month. However, in case of severe flea infestation, retreatment may be necessary earlier than four weeks. Do not re-treat more often than once every seven (7) days. After flea control is obtained, return to a monthly retreatment schedule.

ADDITIONAL INFORMATION

The successive feeding activity of fleas on dogs frequently elicits a hypersensitivity skin disorder known as flea allergy dermatitis (FAD) or flea bite hypersensitivity. Treatment of dogs with Advantage® II Small Dog rapidly kills fleas within 12 hours which may reduce the incidence of this condition.

Advantage® II Small Dog kills existing fleas on dogs within 12 hours. Reinfesting fleas are killed within 2 hours with protection against further flea infestation lasting for four (4) weeks. Pre-existing pupae in the environment may continue to emerge for six (6) weeks or longer depending upon the climatic conditions.

Fleas, flea eggs, and flea larvae in the dog's environment are killed following contact with an Advantage® II Small Dog treated pet. Advantage® II Small Dog provides multi-stage flea control effectively breaking all flea life-cycle stages for quick and lasting control of flea populations.

Advantage® II Small Dog kills adult fleas quickly within 12 hours, inhibits the development of immature flea life stages and prevents them from reaching the biting adult stage.

Advantage® II Small Dog kills [(biting) (chewing)] lice that infest dogs and puppies, and prevents further infestations.

Advantage® II Small Dog is waterproof and remains effective following a shampoo treatment, swimming or after exposure to rain or sunlight.

Monthly treatments are required for optimal control and prevention of fleas.

STORAGE AND DISPOSAL

Do not contaminate water, food or feed by storage or disposal.

Pesticide Storage: Store in a cool, dry place.

Pesticide Disposal and Container Handling: Nonrefillable container. If empty: Do not reuse or refill this container. Place in trash or offer for recycling if available. If partly filled: Call your local solid waste agency or 1-800-422-9874 for disposal instructions. Never place unused product down any indoor or outdoor drain.

Reason To Issue: Revised per EPA letter 4/29/10, and added Date: 09/15/2010

optional text: [Sample – Not for Re)Sale] Supersedes: 04/28/10

LIMITED WARRANTY AND LIMITATION OF DAMAGES

Bayer HealthCare LLC, Animal Health Division warrants that this material conforms to the chemical description on the label. TO THE EXTENT CONSISTENT WITH APPLICABLE LAW, BAYER MAKES NO OTHER EXPRESS OR IMPLIED WARRANTY, INCLUDING ANY OTHER EXPRESS OR IMPLIED WARRANTY OF FITNESS OR MERCHANTABILITY, and no agent of Bayer is authorized to do so except in writing with a specific reference to this warranty. To the extent consistent with applicable law, any damages arising from a breach of this warranty shall be limited to direct damages and shall not include consequential commercial damages such as loss of profits or values, etc.

Net Contents: XX Tubes, each 0.014 fl. oz. (0.4 mL)

[Sample – Not for (Re)Sale]

EPA Est. 11556-DEU-1 EPA Reg. No. 11556-128

Manufactured for
Bayer HealthCare LLC
Animal Health Division
P.O. Box 390
Shawnee Mission, Kansas 66201 USA

Made in Germany

optional text: [Sample - Not for Re)Sale]

NOTE TO REVIEWER: [(Brackets and parentheses indicate alternate language)]

OPTIONAL MARKETING CLAIMS

- For use on dogs and puppies 7 weeks of age and older
- Advantage II contains [imidacloprid], and [an/the] [insect growth regulator] [IGR] [pyriproxyfen]
- A single topical application remains effective for [4 weeks] [a month]
- Convenient, easy to apply topical solution
- Convenient, easy to apply and fragrance free [monthly] [topical solution]
- Once a month topical flea treatment for dogs 7 weeks of age or older
- Advantage II is indicated for the prevention and treatment of fleas on dogs 7 weeks of age and older
- For the treatment and prevention of flea [and lice] infestations
- One treatment prevents further flea infestations for [4 weeks] [a month]
- Kills fleas on dogs within [12] hours and continues to prevent infestations for [four weeks] [a month]
- Kills fleas before they lay eggs
- Larval flea stages in the dog's environment are killed following contact with an Advantage II treated dog
- · Kills larval stages of fleas in the dog's environment
- Kills fleas within [12] hours of application
- Stops existing flea infestations by killing adult fleas
- Prevents [Stops] reinfestations by killing adult fleas before they lay eggs
- [Prevents] [Stops] flea eggs from hatching [into biting adults]
- Effectively breaks the flea life cycle
- Effectively targets all [life] stages of [fleas]
- [Kills] [Controls] all flea life stages
- 3-way flea protection ([kills] [controls] adults, larvae, and eggs)
- [Prevents] [Stops] flea eggs [and flea larvae] from developing into [(biting) (adult)] fleas
- Treatment with Advantage II rapidly kills fleas which may cause flea allergic dermatitis [FAD] or flea bite hypersensitivity
- Flea adulticide, larvicide, and ovicide
- Kills flea eggs
- Controls highly [irritating] [annoying] [flea] [insect] bites
- Controls flea problems
- Provides flea protection
- Controls existing fleas and flea eggs [(plus) (and)] [prevents] future flea infestations in the home
- Starts working through contact

Reason To Issue: Revised per EPA letter 4/29/10, and added Date: 09/15/2010 optional text: [Sample – Not for Re)Sale] Supersedes: 04/28/10

- Use flea [prevention][protection] year-round
- Contains an insect growth regulator (IGR) to kill flea eggs and prevent reinfestation
- Monthly use of Advantage II kills fleas which may cause ([flea allergy dermatitis][flea bite hypersensitivity])
- Multi-stage flea control
- · Prevents fleas on treated dogs from infesting (reinfesting) your home
- · Kills fleas which may serve as intermediate hosts for tapeworms
- Kills [(biting) (chewing)] lice
- For treatment and prevention of [(biting) (chewing)] lice [infestations]
- Stops existing [(biting) (chewing)] lice infestations
- Dual protection against fleas and lice
- Treats, prevents and controls [(biting) (chewing)] lice [infestations]
- Provides effective control of [(biting) (chewing)] lice [infestations]
- Kills [(biting) (chewing)] lice and prevents further infestations
- For treatment and prevention of infestations with [(biting) (chewing)] lice
- · Remains effective after bathing and/or swimming
- Remains effective following swimming and/or shampooing
- Waterproof
- Remains effective after exposure to rain or sunlight
- Fragrance free
- [In child-resistant packaging]

Reason To Issue: Revised per EPA letter 4/29/10, and added

optional text: [Sample - Not for Re)Sale] Su

Date: 09/15/2010 Supersedes: 04/28/10

(Label on Individual Tube)

Advantage® II Small Dog

9.10% Imidacloprid

0.46% Pyriproxyfen

0.014 fl. oz. (0.4 mL)

EPA Reg. No. 11556-128

CAUTION

Keep Out of Reach of Children

Read The Entire Label Before Use

BAYER

Lot No. 0000000

Material to be added to an e-Jacket/Jacket

Reg. No. 11556 -128

Descrip	otion:
1. 🗆	Placement within the e-Jacket/jacket:
	☑ Default: (chronological, top = newest)
	☐ File Location: (PDF page number, i.e., "before page 45")
_	
2. 🗆	Send to Data Extraction contractors this material:
	Newly stamped accepted label
	□ Notification
	□ New CSF
	□ Other:
must Then	ach this coversheet to the top of the material or jacket. It be well organized and clipped together, NOT STAPLED. give the material with this coversheet to staff in the mation Services Center (Room S-4900).
Revi	iewer's Name: <u>Autumn Metzger</u>
Pho	ne: <u>305-5314</u> Division: <u>IRB</u>
Date	e: 40 5/4/10

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460



APR 2 9 2010

OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

Douglas Spilker, Ph.D Bayer HealthCare LLC, Animal Health Division P.O. Box 390 Shawnee Mission, KS 66201-0390

Dear Dr. Spilker:

Subject:

Review new Child Resistant Packaging studies (CRP), amend the opening instructions on the label per the CRP studies submitted and change the primary

brand name

Advantage II Small Dog

EPA Registration No. 11556-128

Decision No. 424618

The labeling referred to above submitted in connection with the Federal Insecticide, Fungicide and Rodenticide, as amended, is acceptable with the following comments and conditions:

Label Comments:

- 1. The primary brand name change from "Advantage Plus 10 for Dogs" to "Advantage II Small Dog" is acceptable.
- 2. On page 4, under "Additional Information," revise the sentence that reads "Treatment of dogs with Advantage II rapidly kills fleas which condition" to read "Treatment of dogs with Advantage II rapidly kills fleas within 12 hours whichcondition" to qualify "rapidly."
- 3. On page 4, under "Additional Information," revise the sentence that reads "Advantage II kills adult fleas quickly, inhibits... adult stage" to read "Advantage II kills adult fleas quickly within 12 hours, inhibits....adult stage" to qualify "quickly."
- 4. On page 4, under the "Storage and Disposal" section, revise the subheadings to read: "Pesticide Storage" and "Pesticide Disposal and Container Handling."
- 5. On page 6, under "Optional Marketing Claims," revise the claim that reads "Starts working by contact" to read "Starts working through contact."

- 6. On page 7, under "Optional Marketing Claims," revise the claim that reads [Dual-Action] [2-way] formula" to qualify what is meant by "dual-action" and "2-way."
- 7. On page 7, under "Optional Marketing Claims," revise the claim that reads "Dual protection (against fleas and lice)" to read "Dual protection against fleas and lice" to qualify what is meant by "dual protection."

Conditions of acceptance:

1. This registration is now time-limited and expires two years from the date this product is first released for shipment.

You must provide the Agency with a projected release for shipment at least 30 days in advance.

- 2. Only one basic confidential statement of formula will be on file for this product at any one time; no alternate formulations or minor formulation amendments will be submitted or approved for this product.
- 3. You must submit quarterly enhanced incident reports and quarterly sales information in doses sold for this product beginning [January 1, April 1, July 1, or October 1, whichever date most closely follows the release for shipment date.]

Please flag any Confidential Business Information as such. Enhanced incident reporting should be submitted to the Product Manager. Quarterly sales information should be submitted to the Registration Division, Immediate Office (attn: Kimberly Nesci).

The following is a list of information that must be included in the quarterly reports for each incident:

EPA Registration Number
Product name (brand name)
Lot #
Where purchased: internet, store, veterinarian
Active Ingredient(s)
Weight range for product

Date on which incident occurred. (mm/dd/yyyy)
State in which the incident occurred. (standard 2 letter abbreviation)
Registrant case #

Species: dog, cat, other (specify)
Breed: (as reported by pet owner)

Age: months or years Sex: M, F, or neutered

Weight: pounds

Primary Route of Exposure: dermal, oral, other animal, inhalation, other Body System: neurological, dermatological, GI, respiratory, ocular, other Major signs noted with separate column for each sign, using standard terminology

Time to Onset: (hours, days)
Treated by veterinarian: yes or no
First time product used: yes or no

Misuse: use on incorrect species, overdose, too frequent dosing, other (describe)

Any known precondition

EPA Severity Code: death, major, moderate, minor Outcome: died, recovered, still treated, unknown

- 4. Along with the enhanced incident reporting, you must submit an analysis of the incidents seen, to include the following details:
 - All incidents should be reported including all minor dermal and ocular irritation reports.
 - Summary table for dogs showing number of incidents of each severity code for each route of exposure. Each incident should only be reported once. If one incident has several routes of exposure, the order should be ocular > oral > dermal. In other words, an incident with both oral and dermal exposure would be reported as oral exposure, and an incident with both ocular and oral exposure would be reported as ocular exposure.
 - A similar summary table for cats (misuse or secondary exposure) showing number of incidents of each severity code for each route of exposure.
 - Summary table for dogs and table for cats showing number of incidents that are believed due to secondary exposure (e.g., multi-pet households).
 - A summary table for dogs showing number of incidents for each severity code for these age ranges: <3 months, 3-6 months, 6-9 months, 9-12 months, 1 yr, 2 yr, 3 yr, 4 yr, 5 yr, 6 yr, 7 yr, 8 yr, 9 yr, 10 yr, 11 yr, 12 yr, 13 yr, 14 yr, 15 yr, >15 yr.
 - A summary table showing the number of dog incidents for each severity code for each pet weight range on the product label.
 - A summary table for dog weight showing number of incidents for each product weight range. This table should show number of incidents in dogs weighing less than that product weight range, number of incidents in dogs in lower half of weight range, number of incidents in dogs in upper half of weight range, and dogs weighing more than the product weight range.
 - Table showing number of incidents for each dog breed.

- Table showing number of incidents in dogs for each clinical sign.
- Table showing number of incidents in dogs for each organ system.
- Report aggregate incidents, but do not combine moderate and minor incidents.

If EPA determines that future mitigation measures are necessary for all pet spot-ons, the Agency will inform registrants. If mitigation measures are necessary, EPA may take regulatory action.

Two copies of the finished labeling must be submitted prior to releasing the product for shipment. If these conditions are not complied with, the registration will be subject to cancellation in accordance with FIFRA sec. 6(e). Your release for shipment of the product constitutes acceptance of these conditions. A copy of your label stamped "Accepted with Comments" is enclosed for your records. If you have any questions regarding this label, please contact Autumn Metzger at (703) 305-5314.

Sincerely,
Very Eague

Venus Eagle

Product Manager 01

Insecticide-Rodenticide Branch Registration Division (7505P)

Reason To Issue:	Minor updates and change primary brand	Date: 04/28/10
	name.	Supersedes: 12/07/09

NOTE TO REVIEWER: [(Brackets and parentheses indicate alternate language)]

Advantage® II Small Dog

Once-A-Month Topical Treatment for Fleas and Lice On Dogs and Puppies 7 Weeks and Older and Weighing 10 lbs. and Under

READ ENTIRE LABEL BEFORE EACH USE

For the Prevention and Treatment of Flea and Lice Infestations [on Dogs]

[Selected optional claims bulleted here from page 6 and/or 7] • • • • • •	ACCEPTED With COMMENTS In EPA Letter Dated: APR 2 9 2010 Under the Federal Insecticide, Fungicide and Rodenticide Act, As amended, for the pesticide Registered under EPA Reg. No: \\S5\Q-1\Z\S		
•			
Active Ingredients	% By Weight		
Imidacloprid	9.10%		
Pyriproxyfen	0.46%		
Other Ingredients	90.44%		
Total	100.00%		
EPA Reg. No. 11556-128	EPA Est. 11556-DEU-I		

KEEP OUT OF REACH OF CHILDREN

CAUTION

[See back panel for First Aid]

[For Directions For Use, and Storage and Disposal (instructions), See supplemental labeling inside]

Page 1 of 8

name. Supersedes: 12/07/09

PRECAUTIONARY STATEMENTS

HAZARDS TO HUMANS

Harmful if swallowed. Causes moderate eye irritation. Avoid contact with eyes or clothing. Wash hands thoroughly with soap and warm water after handling.

HAZARDS TO DOMESTIC ANIMALS

For external use only. Do not use on puppies under 7 weeks of age. As with any product, consult your veterinarian before using this product on debilitated, aged, pregnant or nursing animals. Individual sensitivities, while rare, may occur after using ANY pesticide product for pets. If signs persist, or become more severe, consult a veterinarian immediately. If your animal is on medication, consult your veterinarian before using this or any other product. For consumer questions call 1-800-255-6826. For medical emergencies call 1-800-422-9874.

FIRST AID

Have the product container or label with you when calling a poison control center or doctor, or going for treatment.

IF SWALLOWED: Call a Poison Control Center or doctor immediately for treatment advice. Have person sip a glass of water if able to swallow. Do not induce vomiting unless told to do so by the poison control center or doctor. Do not give anything to an unconscious person.

IF IN EYES: Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye. Call a poison control center or doctor for treatment advice.

IF ON SKIN: Wash with plenty of soap and water.

TO PHYSICIAN: Treat the patient symptomatically.

DIRECTIONS FOR USE

It is a violation of Federal Law to use this product in a manner inconsistent with its labeling.

name. Supersedes: 12/07/09

HOW TO OPEN

1. Being careful not to cut close to the blister cavities, take scissors and cut off one section of the card containing a single tube.

- 2. Take the separated section, and cut into the blister cavity across the small side, close to the cap of the tube.
- 3. Peel off the foil, and take out the tube.
- 4. Repeat steps 1 to 3 for each tube.



HOW TO APPLY

- 1. Use only on dogs. Do not use on other animals.
- 2. Remove one applicator tube from the package. See "HOW TO OPEN" section.
- 3. Hold applicator tube in an upright position. Pull cap off tube.

[Visuals Depicting How to Open Applicator Tube]

- 4. Turn the cap around and place other end of cap back on tube.
- 5. Twist cap to break seal, then remove cap from tube.

[Visuals Depicting Application To Animal]

6. The dog should be standing for easy application. Part the hair on the dog's back, between the shoulder blades, until the skin is visible. Place the tip of the tube on the skin and squeeze the tube to expel the entire contents directly on the skin. Do not get this product in your pet's eyes or mouth.

name. Supersedes: I2/07/09

7. Discard empty tube as described in the Storage and Disposal section.

8. Under normal conditions the product is effective for a month. However, in case of severe flea infestation, retreatment may be necessary earlier than four weeks. Do not re-treat more often than once every seven (7) days. After flea control is obtained, return to a monthly retreatment schedule.

ADDITIONAL INFORMATION

The successive feeding activity of fleas on dogs frequently elicits a hypersensitivity skin disorder known as flea allergy dermatitis (FAD) or flea bite hypersensitivity. Treatment of dogs with Advantage® II rapidly kills fleas which may reduce the incidence of this condition.

Advantage[®] Il kills existing fleas on dogs within 12 hours. Reinfesting fleas are killed within 2 hours with protection against further flea infestation lasting for four (4) weeks. Preexisting pupae in the environment may continue to emerge for six (6) weeks or longer depending upon the climatic conditions.

Fleas, flea eggs, and flea larvae in the dog's environment are killed following contact with an Advantage[®] II treated pet. Advantage[®] II provides multi-stage flea control effectively breaking all flea life-cycle stages for quick and lasting control of flea populations.

Advantage[®] II kills adult fleas quickly, inhibits the development of immature flea life stages and prevents them from reaching the biting adult stage.

Advantage® II kills [(biting) (chewing)] lice that infest dogs and puppies, and prevents further infestations.

Advantage[®] II is waterproof and remains effective following a shampoo treatment, swimming or after exposure to rain or sunlight.

Monthly treatments are required for optimal control and prevention of fleas.

STORAGE AND DISPOSAL

Do not contaminate water, food or feed by storage or disposal.

Storage: Store in a cool, dry place.

Disposal: Nonrefillable container. If empty: Do not reuse or refill this container. Place in trash or offer for recycling if available.

If partly filled: Call your local solid waste agency or I-800-422-9874 for disposal instructions. Never place unused product down any indoor or outdoor drain.

name. Supersedes: 12/07/09

LIMITED WARRANTY AND LIMITATION OF DAMAGES

Bayer HealthCare LLC, Animal Health Division warrants that this material conforms to the chemical description on the label. TO THE EXTENT CONSISTENT WITH APPLICABLE LAW, BAYER MAKES NO OTHER EXPRESS OR IMPLIED WARRANTY, INCLUDING ANY OTHER EXPRESS OR IMPLIED WARRANTY OF FITNESS OR MERCHANTABILITY, and no agent of Bayer is authorized to do so except in writing with a specific reference to this warranty. To the extent consistent with applicable law, any damages arising from a breach of this warranty shall be limited to direct damages and shall not include consequential commercial damages such as loss of profits or values, etc.

Net Contents: ([One][Four] [Six]) 0.014 fl. oz. (0.4 mL) Tubes

EPA Est. 11556-DEU-I EPA Reg. No. 11556-128

Manufactured for
Bayer HealthCare LLC
Animal Health Division
P.O. Box 390
Shawnee Mission, Kansas 66201 USA

Made in Germany

name, Supersedes: 12/07/09

NOTE TO REVIEWER: [(Brackets and parentheses indicate alternate language)]

OPTIONAL MARKETING CLAIMS

- For use on dogs and puppies 7 weeks of age and older
- Advantage II contains [imidacloprid], and [an/the] [insect growth regulator] [IGR]
 [pyriproxyfen]
- A single topical application remains effective for [4 weeks] [a month]
- · Convenient, easy to apply topical solution
- Convenient, easy to apply and fragrance free [monthly] [topical solution]
- Once a month topical flea treatment for dogs 7 weeks of age or older
- Advantage II is indicated for the prevention and treatment of fleas on dogs
 7 weeks of age and older
- · For the treatment and prevention of flea [and lice] infestations
- One treatment prevents further flea infestations for [4 weeks] [a month]
- Kills fleas on dogs within [12] hours and continues to prevent infestations for [four weeks] [a month]
- Kills fleas before they lay eggs
- Larval flea stages in the dog's environment are killed following contact with an Advantage II treated dog
- Kills larval stages of fleas in the dog's environment
- Kills fleas within [12] hours of application
- Stops existing flea infestations by killing adult fleas
- Prevents [Stops] reinfestations by killing adult fleas before they lay eggs
- [Prevents] [Stops] flea eggs from hatching [into biting adults]
- Effectively breaks the flea life cycle
- Effectively targets all [life] stages of [fleas]
- [Kills] [Controls] all flea life stages
- 3-way flea protection ([kills] [controls] adults, larvae, and eggs)
- [Prevents] [Stops] flea eggs [and flea larvae] from developing into [(biting) (adult)] fleas
- Treatment with Advantage II rapidly kills fleas which may cause flea allergic dermatitis [FAD] or flea bite hypersensitivity
- Flea adulticide, larvicide, and ovicide
- Kills flea eggs
- Controls highly [irritating] [annoying] [flea] [insect] bites
- Controls flea problems
- Provides flea protection
- Controls existing fleas and flea eggs [(plus) (and)] [prevents] future flea infestations in the home
- Starts working by contact

name. Supersedes: 12/07/09

• [Dual-Action][2-way] formula

- Use flea [prevention][protection] year-round
- Contains an insect growth regulator (IGR) to kill flea eggs and prevent reinfestation
- Monthly use of Advantage II kills fleas which may cause ([flea allergy dermatitis][flea bite hypersensitivity])
- Multi-stage flea control
- Prevents fleas on treated dogs from infesting (reinfesting) your home
- Kills fleas which may serve as intermediate hosts for tapeworms
- Kills [(biting) (chewing)] lice
- For treatment and prevention of [(biting) (chewing)] lice [infestations]
- Stops existing [(biting) (chewing)] lice infestations
- Dual protection (against fleas and lice)
- Treats, prevents and controls [(biting) (chewing)] lice [infestations]
- Provides effective control of [(biting) (chewing)] lice [infestations]
- Kills [(biting) (chewing)] lice and prevents further infestations
- For treatment and prevention of infestations with [(biting) (chewing)] lice
- Remains effective after bathing and/or swimming
- Remains effective following swimming and/or shampooing
- Waterproof
- Remains effective after exposure to rain or sunlight
- Fragrance free
- [In child-resistant packaging]

name. Supersedes: I2/07/09

(Label on Individual Tube)

Advantage® II Small Dog

9.10% Imidacloprid

0.46% Pyriproxyfen

0.014 fl. oz. (0.4 mL)

EPA Reg. No. 11556-128

CAUTION

Keep Out of Reach of Children

Read The Entire Label Before Use

BAYER

Lot No. 0000000

CHILD-RESISTANT PACKAGING REVIEW Technical Review Branch

IN	1/12/2010 OUT 3/8/2010
RD, TRB, Reviewed by Ros	Salind L. Gross 3/8/2010
EPA Reg. No. or File Symbo	ol <u>11556-125, 11556-127, 11556-128, 11556-130</u>
DP Barcode <u>D372672, 3</u>	372669, 372664, 372662
Decision # <u>424617,42461</u> EPA Petition or EUP No	
Date Division Received12	2/11/2009
Type Product(s) Insecticide	e (flea product)
• •	<u>479321-01,02,03,04; 479322-01,02,03,04; 479323-</u> 01,02,03,04; 479320-01,02,03,04
Product Mgr./Chemical Rev Division <u>RD</u>	riew Mgr/Contact Person <u>RM 01_(Autumn Metzger)</u>
· / ——	ge Plus 20 for Dogs, Advantage Plus 55 for Dogs, ge Plus 10 for Dogs, Advantage Plus 100 for Dogs
Company Name(s) <u>Bayer F</u>	Healthcare LLC
<u>.</u>	Review of CRP studies to determine if they are adequate to support CRP certification for retail blisters of nonchild-resistant tubes.
Active Ingredient(s), PC cod	de, & % <u>Imidacloprid 9.1%</u> Pyriproxyfen 0.46%

Summary of Findings

The CRP certifications submitted December 7, 2009 for EPA Registration No. 11556-125, 11556-127, 11556-128, 11556-130 are acceptable. A screening of CRP studies (MRID numbers 479321-01,02,03,04; 479322-01,02,03,04; 479323-01,02,03,04; 479320-01,02,03,04) revealed the CRP studies associated with the lowest senior adult use effectiveness (SAUE) was MRID number 479322-04 and the lowest child-resistant effectiveness (CRE) was MRID number 479320-03. A comprehensive review was done for the lowest SAUE including the CRE associated with it (MRID numbers 479322-04 & 479322-03); the lowest CRE including the SAUE associated with it (MRID numbers 479320-03 & 479320-04); and the 6 tube 1ml size

SAUE and CRE (MRID numbers 479321-04 & 479321-03) because the size difference between the 0.4ml size reviewed under EPA Reg. No. 11556-RLR and 2.5ml size reviewed here as the lowest SAUE was too large. The results of the comprehensive review for MRID numbers 479322-04 & 479322-03, MRID numbers 479320-04 & 479320-03 indicate these studies pass the CRE sequential test chart and SAUE requirements in 16 CFR 1700.20. For the details of each study refer to the attached summary chart (summarycht11556-125,127,128,130.doc).

Based on the CRE and SAUE values the registrant reported for MRID numbers 479321-01 & 02; 479322-01& 02; 479323-01,02,03,04; 479320-01& 02 along with a computerized analysis of the data these studies pass the CRE sequential test chart and SAUE requirements in 16 CFR 1700.20. For the details of each study refer to the attached summary chart (summarycht11556-125,127,128,130.doc).

In conclusion all the requirements for CRP have been met for EPA Reg. No. 11556-125, 11556-127, 11556-128, and 11556-130. However, the directions on opening the package given to consumers must be identical to those given to the seniors during testing for the blisters. The senior testing directions are on the labels for EPA Reg. No. 11556-125, 11556-127, 11556-128, and 11556-130 dated December 7, 2009. Should any human experience/epidemiological evidence indicate a problem once the product is in the marketplace, the Agency reserves the right to reexamine this data comprehensively and to question the child resistance of the package involved.

Package

The package is a plastic blister with a foil backing containing tubes of product, which the registrant refers to as a tropical foil KISI blister. The blister is the child-resistant packaging, CRP, not the individual tubes.

Toxicity

The toxicity of the product, which contains 9.1% Imidacloprid and 0.46% Pyriproxyfen, is based on toxicity data for a 9.0% Imidacloprid and 0.48% Pyriproxyfen formulation. The acute oral LD₅₀ study MRID 470894-11 (9.0% Imidacloprid and 0.48% Pyriproxyfen) is 1098mg/kg for the female rat, no male rat was used in the study. The toxic or harmful amount for an 11.4 kg child is 12.5g (1098mg/kg x 11.4kg), which is 11.4ml of product (12.5g divided by 1.092g/ml [product density]).

Failure

For the purposes of CRP testing a child failure is access to 12.5g = 11.4ml or 9 blister cavities, whichever is less. A blister cavity failure for the child test was defined as any breach/penetration of the blister cavity, a visible incision or opening made by a

child, or any amount of placebo/water accessed.

A Senior Adult Use Effectiveness failure is failure to open the blister cavity in the prescribed test time of 5 minutes for the first package or 1 minute for the second package, cutting the tube while opening the blister cavity for either the first or second package, or accessing any amount of placebo/water while opening the blister cavity for either the first or second package.¹

Toxicity,	Child	Failure,	and	Package
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Package Size	Toxic/Harmful Amt	Child Failure
4 tubes @ 1ml	12 tubes	9 tubes
6 tubes @ 1ml	12 tubes	9 tubes
4 tubes @ 2.5ml	5 tubes	5 tubes
6 tubes @ 2.5ml	5 tubes	5 tubes
4 tubes @0.4ml	29 tubes	9 tubes
6 tubes @0.4ml	29 tubes	9 tubes
4 tubes @ 4ml	3 tubes	3 tubes
6 tubes @ 4ml	3 tubes	3 tubes

Analysis of Data and Conclusion

The CRP certifications submitted December 7, 2009 for EPA Registration No. 11556-125, 11556-127, 11556-128, 11556-130 are acceptable. A screening of CRP studies (MRID numbers 479321-01,02,03,04; 479322-01,02,03,04; 479323-01,02,03,04; 479320-01,02,03,04) revealed the CRP studies associated with the lowest senior adult use effectiveness (SAUE) was MRID number 479322-04 and the lowest child-resistant effectiveness (CRE) was MRID number 479320-03. A comprehensive review was done for the lowest SAUE including the CRE associated with it (MRID numbers 479322-04 & 479322-03); the lowest CRE including the SAUE associated with it (MRID numbers 479320-03 & 479320-04); and the 6 tube 1ml size SAUE and CRE (MRID numbers 479321-04 & 479321-03) because the size difference between the 0.4ml size reviewed under EPA Reg. No. 11556-RLR and 2.5ml size reviewed here as the lowest SAUE was too large.

Senior Adult Use Effectiveness Study 6 red tube blister 2.5 ml size (MRID

¹ **Note:** Bayer considered a failure to open the tube (for the first or second package) or open the tube and blister cavity in more than in the prescribed test time of 5 minutes for the first package or 1 minute for the second package as a SAUE failure. This is more stringent than the CRP regulations and the SAUE failure definition noted above. The tube is not part of the CR feature. In those situations where the SAUE reported by the company is less than the SAUE determined by Agency computer analysis, the lower SAUE will be reported.

479322-04 which is the lowest SAUE) involved having the test subjects open one blister cavity during a 5 minute test period and a one minute test period. Scissors were made available during testing because the test directions given to the seniors called for their use. The results of the study were 94% SAUE. The study is a pass of the Senior Adult test in 16 CFR 1700.20.

Child Study 6 red tube blister 2.5 ml size (MRID 479322-03) involved giving each child 1 blister card with 6 tubes each containing 2.5 ml of water at the start of the test. A child failure was defined as access to 5 blister cavities as the blister card was the child-resistant feature. Data analysis showed one age calculation error, which involved a 48 month old child reported as 49 months old. This error caused the age distribution of the study to be incorrect. However, the overall results of the study were not affected. Eight children accessed one or more blister cavities. 2 children accessed 6 blister cavities (2 failures), 1 child accessed 3 blister cavities, 2 children accessed 2blister cavities, and 3 children accessed 1 blister cavity. The results were 2 child failures, which is also the lowest CRE. However another study with 2 child failures will be used as the lowest CRE study. This study was a pass according to the child sequential test in 16 CFR 1700.20.

Senior Adult Use Effectiveness Study 6 blue tube blister 4 ml size (MRID 479320-04) involved having the test subjects open one blister cavity during a 5 minute test period and a one minute test period. Scissors were made available during testing because the test directions given to the seniors called for their use. The results of the study were 98% SAUE. The study is a pass of the Senior Adult test in 16 CFR 1700.20.

Child Study 6 blue tube blister 4 ml size (MRID 479320-03 which is the lowest CRE) involved giving each child 1 blister card with 6 tubes each containing 4 ml of water at the start of the test. A child failure was defined as access to 3 blister cavities as the blister card was the child-resistant feature. The electronic version of this study was not submitted correctly on the second CD version of the studies, rather GL26415C a 2007 study was submitted under its name. However, the original CD submitted with hard copy was correctly submitted for GL29115C and was used for this review. Data analysis showed 1 age calculation error, which was a 46 month female reported as 47 months old. However, the subject remained in the same age group so the age and sex distribution remains acceptable. Eleven children accessed one or more blister cavities. 2 children accessed 3 blister cavities (2 failures), 3 children accessed 2 blister cavities, and 6 children accessed 1 blister cavity. The results were 2 child failures. This study was a pass according to the child sequential test in 16 CFR 1700.20.

Senior Adult Use Effectiveness Study 6 turquoise tube blister 1 ml size (MRID 479321-04) involved having the test subjects open one blister cavity during a 5 minute test period and a one minute test period. Scissors were made available during

testing because the test directions given to the seniors called for their use. The results of the study were 96% SAUE. The study is a pass of the Senior Adult test in 16 CFR 1700.20.

Child Study 6 turquoise tube blister 1 ml size (MRID 479321-03) involved giving each child 2 blister cards with 6 tubes each containing 1 ml of water at the start of the test. A child failure was defined as access to 9 blister cavities as the blister card was the child-resistant feature. The company data summary incorrectly reported the results, but the raw data in the hard copy was correct and agreed with the computer analysis of the data. 12 children accessed one or more blister cavities. 1 child opened 12 blister cavities (a failure), 1 child opened 4 blister cavities, 1 child opened 3 blister cavities, 4 children opened 2 blister cavities, and 5 children opened 1 blister cavity. The results were one child failure. This study was a pass according to the child sequential test in 16 CFR 1700.20.

Based on the CRE and SAUE values the registrant reported for MRID numbers 479321-01 & 02; 479322-01& 02; 479323-01,02,03,04; 479320-01& 02 along with a computerized analysis of the data these studies pass the CRE sequential test chart and SAUE requirements in 16 CFR 1700.20. For the details of each study refer to the attached summary chart (summarycht11556-125,127,128,130.doc).

In conclusion all the requirements for CRP have been met for EPA Reg. No. 11556-125, 11556-127, 11556-128, and 11556-130. However, the directions on opening the package given to consumers must be identical to those given to the seniors during testing for the blisters. The senior testing directions are on the labels for EPA Reg. No. 11556-125, 11556-127, 11556-128, and 11556-130 dated December 7, 2009. Should any human experience/epidemiological evidence indicate a problem once the product is in the marketplace, the Agency reserves the right to reexamine this data comprehensively and to question the child resistance of the package involved.

CRPdatasummarycht

Chemical - Pyriproxyfen 0.46% Imidacloprid 9. t% March 5, 20 t0

Company Name Bayer Healthcare LLC

A **Senior Adult Use Effectiveness (SAUE)** failure is failure to open the blister cavity in the prescribed test time of 5 min. for the 1st pkg or t min. for the 2nd pkg, cutting the tube while opening the blister cavity for either the tst or 2nd pkg, or accessing any amount of placebo/water while opening the blister cavity for either the 1st or 2nd pkg. **Note:** Bayer considered a failure to open the tube (for the tst or 2nd pkg) or open the tube and blister cavity in more than in the prescribed test time of 5 min. for the tst pkg or t min. for the 2nd pkg as a SAUE failure. This is more stringent than the CRP regulations and the SAUE failure definition noted above. The tube is not part of the CR feature. In those situations where the SAUE reported by the company is less than the SAUE determined by Agency computer analysis, the lower SAUE will be reported.

A child failure is access to t2.5g = tt.4ml for Product Density 1.092g/ml or 9 tubes, whichever is less

A blister cavity failure is any breach/penetration of the blister cavity, a visible incision or opening made by a child, or any amount of placebo/water accessed. Access to a toxic or harmful amt = $t2.5q = 1.098g/kg \times t \cdot t.4kg$ (MRID 470894-1 t oral LD₅₀) = 1 t.4ml for Product Density 1.092g/ml

% AI - Pyriproxyfen 0.46% Imidacloprid 9. t%

EPA REG#	MRID	PKG Description Include ml per Pkg Blister is CR feature not tube.	# Pkges	Company	Company Data		ta	Conclusion
		# unit/pkg, child fail = # units, color, tox/harm = #units	Child Get at Begin Test	CRE blister cavity = bc	SAUE	Comprehe nsive Review & why	Only Compu ter Analysi s	include CRE & SAUE via computer analysis
11556-125	479321-02 GL29118A dog product	4 turquoise tube @ 1ml in tropical foil (KISI) blister. Water placebo in tube. Tox/harm = 12 tubes, child fail = 9 tubes			99% 1fail pkg B open (cut tube)		х	CRP Certification is ok. Label dated 12/7/09 same CRP directions as in study. Data Analysis showed 4 age calcn errors [a 59 yr old female was reported as 58 yrs old, a 57yr old female was reported as 58 yrs old, a 64 yr old female was missing the test date, but it was in the hard copy of data and the age was correct, a 49 yr old male was reported as 52 years old.] There are only 99 test subjects, a 49 yr old is not part of the senior test panel. The age distribution is off. The results are still a pass of the SAUE in 16 CFR 1700.20.

EPA REG#	MRID	PKG Description Include ml per Pkg Blister Is CR feature not tube.	# Pkges	Company	Data	ata Data		Conclusion
		# unit/pkg, child fail = # units, color, tox/harm = #units	Child Get at Begin Test	CRE blister cavity = bc	SAUE	Comprehe nsive Review & why	Only Compu ter Analysl s	include CRE & SAUE via computer analysis
11556-125	479321-01 GL29118C dog product	4 turquoise tube @ 1ml in tropical foil (KISI) blister. Water placebo in tube. Tox/harm = 12 tubes, child fail = 9 tubes	3 blisters with 4 tubes each	0 Fail = Pass 50 child test. 4 children open ≥ 1bc. 2 children open 4bc, 1 child open 3bc, 1 child open 1bc			х	CRP Certification is ok. Data Analysis showed 2 age calcn errors [a 48 month old male was reported as 49 months old, a 47 month old male was reported as 48 months old.] The age distribution is off. 4 children open≥ 1bc. 2 children open 4bc, 1 child open 3bc, 1 child open 1bc. No child failures. Study is a pass of the child test according to sequential chart in 16 CFR 1700.20.
11556-125	479321-04 GL29119A dog product	6 turquoise tube @ 1mi in tropical foil (KISI) blister. Water placebo in tube. Tox/harm = 12 tubes, child fail = 9 tubes			96% 3 fail open pkg A (1 cut tube, 2 no open tube), 1 fail open pkg B in 60 sec	X 0.4 - 2.5ml too lg. So 1ml. Did Comprehe nsive rev 0.4ml in EPA Reg # 11556- RLR (MRID 479252-03 & 04)		CRP Certification is ok. Label dated 12/7/09 same CRP directions as in study. SAUE is 96%. The study is a pass of the senior test in 16 CFR 1700.20.

EPA REG#	MRID	PKG Description include mit per Pkg Bilster is CR feature not tube.	# Pkges	Company Data		Company Data		Company Data		Dat	а	Conclusion
		# unit/pkg, child fail = # units, color, tox/harm = #units	Child Get at Begin Test	CRE blister cavity = bc	SAUE	Comprehe nsive Review & why	Only Compu ter Analysi s	include CRE & SAUE via computer analysis				
11556-125	479321-03 GL29119C dog product	6 turquoise tube @ 1ml in tropical 1oil (KISI) blister. Water placebo in tube. Tox/harm = 12 tubes, child fall = 9 tubes	2 blisters with 6 tubes each	1 Fail = Pass 50 child test. 12 children opened ≥ 1bc. 1 child opened 12 bc (a failure), 1 child opened 4bc, 1 child opened 3bc, 4 children opened 2bc, 5 children opened 1bc.		X 0.4 - 2.5mt too Ig. So 1ml. Did Comprehe nsive rev 0.4ml in EPA Reg # 11556- RLR (MRID 479252-03 & 04)		CRP Certification is ok. The company data summary incorrectly reported 14 children opened ≥ 1bc and incorrectly reported the individual numbers of children opening certain numbers of bc, but the raw data agreed with our Computer Analysis. 12 children opened ≥ 1bc. 1 child opened 12 bc (a failure), 1 child opened 4bc, 1 child opened 3bc, 4 children opened 2bc, 5 children opened 1bc. There was 1 child failure. The study is a pass of the child test according to sequential chart in 16 CFR 1700.20.				
11556-127	479322-02 GL29116A dog product	4 red tube @ 2.5mt in tropical foil (KISt) blister. Water placebo in tube. Tox/harm = 5 tubes, child fail = 5 tubes			96% 31ail open pkg A (2 cut tube, 1 no open tube) 1 fail open pkg B in 60 sec		х	CRP Certification is ok. Label dated 12/7/09 same CRP directions as in study. Data Analysis showed 1age calcn error [a female reported as 55 yrs old was really of indeterminate age due to birth date 5/21/2024.] Therefore the age distribution is off. The results are still a pass of the SAUE in 16 CFR 1700.20.				
11556-127	479322-01 GL29116C dog product	4 red tube @ 2.5ml in tropical foil (KISI) blister. Water placebo in tube. Tox/harm = 5 tubes, child fail = 5 tubes	2 blisters with 4 tubes each	0 Fail = Pass 50 child test. 6 children open ≥ 1bc. 1 child open 3bc, 2 children open 2bc, 3 children open 1bc.			X	CRP Certification is ok. The electronic version of this study was not submitted correctly on the 2 nd version of the studies, rather GL26416C a 2007 study was submitted under its name. However, the original CD submitted with hard copy was correctly for GL 29116C and was used for this review. Data Analysis showed 1age calcn error [a 45 month old female was reported as 46 months old]. However, the subject remained In the same age grp, the age & sex distribution remains ok. 6 children open ≥ 1bc. 1 child open 3bc, 2 children open 2bc, 3 children open 1bc. No child failures. Study is a pass of the child test according to sequential chart in 16 CFR 1700.20.				

EPA REG#	MRIĐ	PKG Description Include ml per Pkg Blister is CR feature not tube.	# Pkges	Company Data		Data		Conclusion
		# unit/pkg, child fail = # units, color, tox/harm = #units	Child Get at Begin Test	CRE blister cavity # bc	SAUE	Comprehe nsive Review & why	Only Compu ter Analysi s	include CRE & SAUE via computer analysis
11556-127	479322-04 GL29117A dog product	6 red tube @ 2.5ml in tropical foil (KISI) blister. Water placebo in tube. Tox/harm =5 tubes, child fail = 5 tubes			94% 3 fail open pkg A (2 cut tube, 1 no open tube) 1 fail open pkg B (cut tube), 2 fail pkg B open in 60 sec	X lowest SAUE & also lowest CRE		CRP Certification is ok. Label dated 12/7/09 same CRP directions as in study. SAUE is 94%. The study is a pass of the senior test in 16 CFR 1700.20.
11556-127	479322-03 GL29117C dog product	6 red tube @ 2.5ml in tropical foil (KISI) blister. Water placebo in tube. Tox/harm = 5 tubes, child fall = 5 tubes	1 blister with 6 tubes	2 Fail = Pass 50 child test. 8 children open ≥ 1bc. 2 children open 6bc (2 failures), 1 child open 3bc, 2 children open 2bc, 3 children open 1bc.		X lowest CRE & also lowest SAUE		CRP Certification is ok. Data Analysis showed 1age calcn error (a 48 month female was reported as 49 months old). The age distribution is off. 8 children open ≥ 1bc. 2 children open 6bc (2 failures), 1 child open 3bc, 2 children open 2bc, 3 children open 1bc. There were 2 child failures. The study is a pass of the child test according to sequential chart in 16 CFR 1700.20.
11556-128	479323-02 GL29120A dog product	4 green tube @ 0.4ml in tropical foil (KISI) blister. Water placebo in tube. Tox/harm = 29 tubes, child fail = 9 tubes			95% 3 fail open pkg A (1 cut bc in half, 1 cut tube, 1 no open tube) 1 fail open pkg B (no open tube) 1 fail open pkg B in 60 sec		X	CRP Certification is ok. Label dated 12/7/09 same CRP directions as in study. Data Analysis showed 1age calcn error (a 51 year female was reported as 52 years old). However, the subject remained in the same age grp, the age & sex distribution remains ok. The maximum number of test subjects per test site was exceeded for one test site. The results are still a pass of the SAUE in 18 CFR 1700.20.

EPA REG#	MRID	PKG Description include mil per Pkg Blister is CR feature not tube.	# Pkges	Company Data		Data		Conclusion
		# unit/pkg, child fail = # units, color, tox/harm = #units	Child Get at Begin Test	CRE blister cavity = bc	SAUE	Comprehe nsive Review & why	Only Compu ter Analysi s	include CRE & SAUE via computer analysis
11556-128	479323-01 GL29120C dog product	4 green tube @ 0.4ml in tropical foil (KISI) blister. Water placebo in tube. Tox/hamn = 29 tubes, child fail = 9 tubes	3 blisters with 4 tubes each	0 Fail = Pass 50 child test. 9 children open ≥ 1bc. 1 child open 4bc, 1 child open 3bc, 2 children open 2bc, 5 children open 1bc,			X	CRP Certification is ok. Data Analysis showed 1age calcn error [a 45 month male was reported as a 44 month old). The age distribution is off. 9 children open ≥ 1bc. 1 child open 4bc, 1 child open 3bc, 2 children open 2bc, 5 children open 1bc. No child 1ailures. Study Is a pass of the child test according to sequential chart in 16 CFR 1700.20.
11556-128	479323-04 GL29121A dog product	6 green tube @ 0.4ml in tropical foil (KISI) blister. Water placebo in tube. Tox/hamn = 29 tubes, child fail = 9 tubes			99% 1 fail pkg A (cut tube)		X	CRP Certification is ok. Label dated 12/7/09 same CRP directions as in study. SAUE is 99%. The study is a pass of the senior test in 16 CFR 1700.20.
11556-128	479323-03 GL29121C dog product	6 green tube @ 0.4ml in tropical foil (KISI) blister. Water placebo in tube. Tox/harm = 29 tubes, child fail = 9 tubes	2 blisters with 6 tubes each	0 Fail = Pass 50 child test. 5 children open ≥ 1bc. 1 child open 3bc, 4 children open 1bc.			x	CRP Certification is ok. 5 children open ≥ 1bc. 1 child open 3bc, 4 children open 1bc. No child failures. Study is a pass of the child test according to sequential chart in 16 CFR 1700.20.
11556-130	479320-02 GL29114A dog product	4 blue tube @ 4ml in tropical foil (KISI) blister. Water placebo in tube. Tox/ham = 3 tubes, child fail = 3 tubes			98% 1 fail pkg A (cut tube), 1 fail pkg B in 60 sec		Х	CRP Certification is ok. Label dated 12/7/09 same CRP directions as in study. SAUE is 98%. The study is a pass of the senior test in 16 CFR 1700.20.
11556-130	479320-01 GL29114C dog product	4 blue tube @ 4ml in tropical foil (KISI) blister. Water placebo in tube. Tox/harm = 3 tubes, chlid fail = 3 tubes	1 blister with 4 tubes	0 Fail = Pass 50 child test. 10 children open ≥ 1bc. 1 child open 2bc, 9 children open 1bc.			X	CRP Certification is ok. Data Analysis showed 2 age calcn errors [a 45 month male was reported as 46 months old, a 44 month female was reported as 43 months old). However, the subjects remained in the same age grp, the age & sex distribution remains ok. 10 children open ≥ 1bc. 1 child open 2bc, 9 children open 1bc. No child failures. Study is a pass of the child test according to sequential chart in 16 CFR 1700.20.

EPA REG#	MRID	PKG Description Include mi per Pkg Blister is CR feature not tube.	# Pkges	Company Data		Data		Conclusion
	: E	# unit/pkg, child fail = # units, color, tox/harm = #units	Child Get at Begin Test	CRE blister cavity ≕ bc	SAUE	Comprehe nsive Review & why	Only Compu ter Analysi s	include CRE & SAUE via computer analysis
11556-130	479320-04 GL29115A dog product	6 blue tube @ 4ml in tropical foil (KISI) blister. Water placebo in tube. Tox/harm = 3 tubes, child fail = 3 tubes			98% 2 fail open pkg B in 60 sec	X SAUE associated with lowest CRE and Igest size		CRP Certification is ok. Label dated 12/7/09 same CRP directions as in study. SAUE is 98%. The study is a pass of the senior test in 16 CFR 1700.20.
11556-130	479320-03 GL29115C dog product	6 blue tube @ 4ml in tropical foil (KISI) blister. Water placebo in tube. Tox/harm = 3 tubes, child fail = 3 tubes	1 bilister with 6 tubes	2 Fail = Pass 50 child test. 11 children open ≥ 1bc. 2 child open 3bc (2 failures), 3 children open 2bc, 6 children open 1 bc.		X lowest CRE and Igest size		CRP Certification is ok. The electronic version of this study was not submitted correctly on the 2 nd version of the studies, rather GL26415C a 2007 study was submitted under its name. However, the original CD submitted with hard copy was correctly for GL29115C and was used for this review. Data Analysis showed 1 age calcn error [a 46 month female was reported as 47 months old[. However, the subject remained in the same age grp, the age & sex distribution remains ok. 11 children open ≥ 1bc. 2 child open 3bc (2 failures), 3 children open 2bc, 6 children open 1 bc. There were 2 child failures. The study is a pass of the child test according to sequential chart in 16 CFR 1700.20.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460



APR 2 9 2010

OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

Douglas Spilker, Ph.D Bayer HealthCare LLC, Animal Health Division P.O. Box 390 Shawnee Mission, KS 66201-0390

Dear Dr. Spilker:

Subject:

Request for Determination of need for Child Resistant Packaging studies (CRP)

for single dose sample packaging

Advantage II Small Dog, EPA Registration No. 11556-128

Advantage II Medium Dog, EPA Registration No. 11556-125

Advantage II Large Dog, EPA Registration No. 11556-127

Advantage II Extra Large Dog, EPA Registration No. 11556-130

As indicated in the CRP review dated 3/8/10, a single tube size of any of the products would not contain a toxic or harmful amount of the product and therefore CRP is not required at this time.

However, "Should any human experience/epidemiological evidence indicate a problem once the product is in the marketplace, the Agency reserves the right to reexamine this data comprehensively and to question the need for child resistance of the package involved."

A copy of the review was provided at our meeting on April 27, 2010. Should you have any questions, please contact Autumn Metzger at 703-305-5314 or metzger.autumn@epa.gov.

Vienez Eager

Venus Eagle

Product Manager 01

Insecticide-Rodenticide Branch Registration Division (7505P)

CHILD-RESISTANT PACKAGING REVIEW Technical Review Branch

IN <u>2/23/2010</u> OUT <u>.3/8/2010</u>
RD, TRB, Reviewed by Rosalind L. Gross 3/8/2010
EPA Reg. No. or File Symbol <u>11556-125, 11556-127, 11556-128, 11556-130,</u> <u>11556-RLN, 11556-RLR, 11556-RLE</u>
DP Barcode <u>D374528 (for 11556-130)</u>
Decision # <u>424615 (for 11556-130)</u> EPA Petition or EUP No
Date Division Received 2/3/2010
Type Product(s) Insecticide (flea product)
Data Accession No(s).
Product Mgr./Chemical Review Mgr/Contact Person <u>RM 01 (Autumn Metzger)</u> Division <u>RD</u>
Product Name(s) Advantage Plus 20 for Dogs, Advantage Plus 55 for Dogs, Advantage Plus 10 for Dogs, Advantage Plus 100 for Dogs, Advantage IGR 5, Advantage IGR 9, Advantage IGR 18,
Company Name(s) Bayer Healthcare LLC
Submission Purpose Review of toxicity data and CRP regulations to determine if single nonchild-resistant tubes are subject to CRP.
Active Ingredient(s), PC code, & % Imidacloprid 9.1% Pyriproxyfen 0.46%

Summary of Findings

While CRP is indicated based on residential use and the acute oral LD $_{50}$, the actual amount of product in a single tube for these 7 products (EPA Registration Numbers 11556-125, 11556-127, 11556-128, 11556-130, 11556-RLN, 11556-RLR, and 11556-RLE) is less than a toxic and harmful amount for an 11.4 kg child. Therefore, a single tube for any of these 7 products in the sizes noted in the table herein (4ml maximum size) is not subject to CRP. Any outer packaging on these tubes resembling CRP especially the CRP being used for the 4 or 6 tube configurations will be construed as voluntary CRP and necessitate CRP testing for each tube size, CRP certification, and amendment of the pertinent registrations.

Should any human experience/epidemiological evidence indicate a problem once the product is in the marketplace, the Agency reserves the right to reexamine this data comprehensively and to question the need for child resistance of the package involved.

<u>Package</u>

The package consists of individual tubes, which are not child-resistant packaging (CRP).

Toxicity

The toxicity of the product, which contains 9.1% Imidacloprid and 0.46% Pyriproxyfen, is based on toxicity data for a 9.0% Imidacloprid and 0.48% Pyriproxyfen formulation. The acute oral LD₅₀ study MRID 470894-11 (9.0% Imidacloprid and 0.48% Pyriproxyfen) is 1098mg/kg for the female rat, no male rat was used in the study. The toxic or harmful amount for an 11.4 kg child is 12.5g (1098mg/kg x 11.4kg), which is 11.4ml of product (12.5g divided by 1.092g/ml [product density]).

Toxicity and CRP

The CRP regulations (40 CFR 157.22) indicate that a product for residential use with an acute oral LD $_{50}$ of 1.5g/kg or less is required to be in CRP. All 7 of these products meet these criteria. However, CRP is intended to prevent children under 5 years of age from opening or obtaining a toxic or harmful amount of a substance in a reasonable time (40 CFR157.21). A toxic or harmful amount is access to 12.5g = 11.4ml. None of these 7 products would contain a toxic or harmful amount in one tube as is shown in the table below. The maximum amount of product in the largest tube (4ml) is $4ml \times 1.092g/ml = 4.37g$.

EPA Reg #	Tube Color & Size	Toxic/Harmful Amt 12.5g = 11.4ml	Child Failure (for CRP testing)		
11556-125	1 turquoise tube @ 1ml	12 tubes	9 tubes		
11556-127	1 red tube @ 2.5ml	5 tubes	5 tubes		
11556-128	1 green tube @0.4ml	29 tubes	9 tubes		
11556-130	1 blue tube @ 4ml	3 tubes	3 tubes		
11556-RLN	1 turquoise tube @ 0.23ml	50 tubes	9 tubes		
11556-RLR	1 orange tube @0.4ml	29 tubes	9 tubes		
11556-RLE	1 purple tube @0.8ml	15 tubes	9 tubes		

Analysis of Data and Conclusion

While CRP is indicated based on residential use and the acute oral LD $_{50}$, the actual amount of product in a single tube for these 7 products (EPA Registration Numbers 11556-125, 11556-127, 11556-128, 11556-130, 11556-RLN, 11556-RLR, and 11556-RLE) is less than a toxic and harmful amount for an 11.4 kg child. Therefore, a single tube for any of these 7 products in the aforementioned sizes in the table above (4ml maximum size) is not subject to CRP. Any outer packaging on these tubes resembling CRP especially the CRP being used for the 4 or 6 tube configurations will be construed as voluntary CRP and necessitate CRP testing for each tube size, CRP certification, and amendment of the pertinent registrations.

Should any human experience/epidemiological evidence indicate a problem once the product is in the marketplace, the Agency reserves the right to reexamine this data comprehensively and to question the need for child resistance of the package involved.

NOTE TO FILE:

These notifications, dated 4/9/10 were all superseded by a Label Amendment stamped 4/29/10 and closed out as so in OPPIN.

Autumn Metzger 4/29/10

Please read instructions on reverse before compuding	form.	Form Approved.	⊶MB No. 2070-0080	Print Form			
EPA Environmental Pi	d Stotes rotection Age in, DC 20460	ncy ×	Registration Amendment Other	OPP Identifier Number			
Ap	plication for i	Pesticide - Section	I				
1. Company/Product Number 11556-128		2. EPA Product Menager Venus Eagle		pposed Classification			
4. Company/Product (Name) Advantage Plus 10 for Dogs		PM# X None Restric					
5. Name and Address of Applicant (Include ZIP Code) 8 ayer HealthCare LLC, Animal Health Division P.O. Box 390 Shawnee Mission, KS 66201-0390 Check if this is a new address	H	6. Expedited Review. In accordance with FIFRA Section 3(c)(3) (b)(i), my product is similar or identical in composition and labeling to: EPA Reg. No Product Name					
	Sec	tion - II					
Amendment - Explain below. Resubmission in response to Agency letter dat Notification - Explain below.	ed	Final printed label Agency letter det "Me Too" Applica Other - Explain be	ed ation,				
Explanation: Use additional pagets) If nacessary. I Notification of addition of an Alternate Brand Na See attached for detailed explanation. Contact: o	me for subject pro loug.spilker.b@ba	oduct. yer.com					
	Sec	tion - III					
Meterial This Product Will Be Pockaged In:							
Child-Resistent Packaging Yes* No Value ×	Woter Soluble Pockeging Yes X No If "Yes" No, per 2. Type of Container Metal Massic Glass Paper						
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!	Sizejs) Reteil Contei 6-0,4ml tube	On label					
6. Manner in Which Lebel ie Affixed to Product	Lithograph Peper gluod Stenciled	Other					
		ion - IV					
1. Contact Point Complete items directly below for it	dentification of indiv	idual to be contacted, if nec	essary, to process this	app(ication.)			
Neme Douglas A. Spilker, Ph D.	Title EPA Reg	ı. Affairs Manager	Talaphan 913-268	e No. (Include Ares Code) -2751			
I certify that the statements i have made on thi i acknowledge that any knowingly felse or misle both under applicable law.	Certification s form and all attack seding statement ma	nments thereto are true, acc sy be punishable by line or in	urata and complete.	8. Dete Application Received ့ (Šှိုamped)			
2. Signature Defle A. Spiller		. Affairs Manager	ς ς. (δείτες (δείτες (δείτες)				
4. Typed Nams Douglas A. Spilker, Ph D.	5, Oate	9 April 2010					

ATTACHMENT FOR APPLICATION FOR PESTICIDE REGISTRATION April 9, 2010

Advantage® Plus 10 for Dogs (EPA Reg. No. 11556-128)

Notification of Alternate Brand Name

In addition to the primary brand name - Advantage® Plus 10 for Dogs - we are notifying the Agency we plan to use the following alternate brand name for this product:

Advantage II Small Dog

As described in PR Notice 98-10, section "A. Brand Names – A registrant may change the primary brand name and add or change one or more alternate brand names by notification." Therefore pursuant to PRN 98-10, Bayer Healthcare LLC, Animal Health Division, is adding the alternate brand name - Advantage II Small Dog - to the file for its product Advantage Plus 10 for Dogs (EPA Reg. No. 11556-128).

This notification is consistent with the provisions of PR Notice 98-10 and EPA regulations at 40 CFR 152.46 and no other changes have been proposed for the labeling or the confidential statement of formula for this product. Bayer understands that it is a violation of 18 U.S. C. Sec. 1001 to willfully make any false statement to EPA. Bayer further understands that if this notification is not consistent with the terms of PR Notice 98-10 and 40 CFR 152.46, this product may be in violation of FIFRA and Bayer may be subject to enforcement action and penalties under sections 12 and 14 of FIFRA.

Page 1of I

Bayer HealthCare Animal Health



Via Federal Express 04/09/10

Document Processing Desk (NOTIF)
Office of Pesticide Programs (7504P)
U.S. Environmental Protection Agency
Room S-4900, One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202-4501

Enclosure:

Application for Pesticide Notification for:

Advantage Plus 10 for Dogs (11556-128) Advantage Plus 20 for Dogs (11556-125) Advantage Plus 55 for Dogs (11556-127) Advantage Plus 100 for Dogs (11556-130) Bayer HealthCare LLC Animal Health P.O. Box 390 Shawnee Mission, KS 66201 Advantage Plus Products for Dogs - Request for Change in Primary Brand Names Doug Spilker

to:

Autumn Metzger 04/28/2010 03:32 PM

Venus Eagle, Kable Davis

Show Details

Dear Ms. Metzger,

This email is to request changes in the primary brand names of the following registrations of Bayer HealthCare, Animal Health Products:

EPA Reg. No.	From	<u>To</u>
11556-128	Advantage Plus 10 for Dogs	Advantage II Small Dog
11556-125	Advantage Plus 20 for Dogs	Advantage II Medium Dog
11556-127	Advantage Plus 55 for Dogs	Advantage II Large Dog
11556-130	Advantage Plus 100 for Dogs	Advantage II Extra Large Dog

We understand from our meeting with the Agency on 4/27/10 that these name changes are acceptable to the Agency. Revised draft labeling with these new primary brand names will be sent to you in a separate email.

If you need anything further to appropriately make this official change to the respective registration files, please let me know.

Best regards,

Doug

Douglas A. Spilker, Ph.D. Manager - EPA Reg. Affairs BAYER HEALTHCARE LLC ANIMAL HEALTH

Office: +1 913-268-2751 Mobile: +1 816-506-3102 Fax: +1 913-268-2135

Email: doug.spilker.b@bayer.com

Address:

P.O. Box 390

Shawnee Mission, KS 66201-0390

Country: USA

Bayer Animal Health "Protecting.Curing.Caring...Together"

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For alternate languages please go to http://bayerdisclaimer.bayerweb.com



Advantage II Products - revised labeling

Doug Spilker o Autumn Metzger

04/28/2010 03:55 PM

Cc: Kable Davis, Venus Eagle

View: (Mail Threads)

Dear Ms. Metzger,

Please find attached appropriately revised draft labeling for the four Advantage II products for dogs (11556-125. -127, -128, -130). You will note, that the newly requested primary brand names have been used (see separate email of 4/28/10). As you requested in our meeting yesterday, these labels have been revised according to your comments given to me in the aforementioned meeting. In addition to those comments, I have made a few other minor revisions, that conform to current EPA format and labeling requirements: a) put the signal word in all CAPS (page 1), b) better separated the headings in the Precautionary statements (page 2), c) added the words "Net Contents" (page 5) and d) added single tube to the list of sizes (page 5). As you will recall, the DER from Ms. Gross allowed this single tube addition. I hope that these minor changes do not delay the processing of the acceptance of these labels.

If you need anything further, please call.

Best regards, Doug

Douglas A. Spilker, Ph.D. Manager - EPA Reg. Affairs BAYER HEALTHCARE LLC ANIMAL HEALTH Office: +1 913-268-2751

Mobile: +1 816-506-3102 Fax: +1 913-268-2135

Email: doug.spilker.b@bayer.com

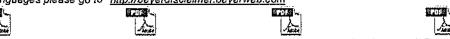
Address: P.O. Box 390 Shawnee Mission, KS 66201-0390

Country: USA

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For alternate tanguages please go to http://beyerdiscleimer.bayerweb.com



Advantage II Small Dog f.pdf Advantage If Medium Dog f.pdf Advantage II Large Dog f.pdf Advantage II Extra Large Dog f.pdf

Doug Spilker/SHAWN/AGCHEM/US /BAYER

03/31/2009 02:t5 PM

To davis.kable@epa.gov

cc Harish

Chopade/SHAWN/AGCHEM/US/BAYER@BAYER-US-NOT

EŞ

bcc Douglas

Hutchens/SHAWN/AGCHEM/US/BAYER@BAYER-US-NOT

ES; Bruce

Martin/SHAWN/AGCHEM/US/BAYER@BAYER-US-NOTES;

Dan

Ciszewski/SHAWN/AGCHEM/US/BAYER@BAYER-US-NOT

ES

Subject CRP Discussion with Dr. Gross

Bo.

Just a note. Rosalind Gross called today (~9:30 CDT), and Dr. Chopade (Bayer) and I spoke with her regarding her input on the document we recently (3/30/09) sent on the CRP testing. Since she called us, I assume you gave her the go-ahead. She had three basic comments to improve our testing:

- We should use the most recent acute oral toxicity study (Bayer Report No. 75922; MRID 47089411) to calculate the Toxic Dose, rather than the one listed in the Reference - Page 1.
- In the Tube Failure Criterion, it should be considered a failure if the child has access to any amount of water (from the tube).
- In the Tube Failure Criterion (adults), it should be considered a failure if the participant opens the
 package improperly, that is not using scissors. How this should be discussed with Great Lakes
 Marketing (contractor).

Since this was just guidance from her, it is our understanding that no additional action is needed by us, unless we have further questions.

For your information, Doug

Doug Spliker
Manager - EPA Reg. Affairs
BAYER HEALTHCARE LLC
ANIMAL HEALTH
Office: +1 913-268-2751

Mobile: +1 816-506-3102 Fax: +1 913-268-2135

Email: doug.spilker.b@bayer.com

Address: P.O. Box 390 Shawnee Mission, KS 66201-0390 Country: USA

Bayer Animal Health "Powered by People, Driven by Science"



Davis.Kable@epamail.epa.go v 03/31/2009 04:52 AM To Doug Spilker <doug.spilker.b@bayer.com>

pcc

Subject Re: CRP Testing for Revised Packaging of Advantage Plus Products

Excellent. Thanks, Doug. I will forward this information on. Have a great, Tuesday. Во Kable Bo Davis, MS Entomologist U.S. Environmental Protection Agency Insecticide-Rodenticide Branch Registration Division [7505P) 1200 Pennsylvania Ave. NW Washington, DC 20460 Tel: 703 306-0415 Fax: 703 305-6596 Email: davis.kable@epa.gov | From: [Doug Spilker < doug.spilker.b@bayer.com> To: 1 |Kable Davis/DC/USEPA/US@EPA [Cc: |Harish Chopade <harish.chopade.b@bayer.com>

03/30/2009 03:25 PM	
> Subject: >	
> CRP Testing for Revised Packaging of Advantage Plus Products	

Dear Mr. Davis,
Reference is made to the meeting of March 4, 2009 (BAH: D. Spilker;
EPA: B. Davis, V. Eagle and R. Gross), which included a discussion on
Advantage Plus for Dogs (11556-125, -127, -128, -130) and our plans to
develop revised packaging for these products, as well as for the
yet-to-be submitted Advantage IGR for Cats product. As you will recall,
these products require child-resistant packaging. As we discussed, we
understand that the full battery of tests with children and adult
seniors, as well as with all package sizes (colors) and all package
configurations (4-packs and 6-packs) is required. We will conduct these
tests as before with Great Lakes Marketing Company, Toledo, Ohio.

In the aforementioned meeting, we discussed with Dr. Rosalind Gross the CRP Testing plans. In that conversation, Dr. Gross requested we send her some specific information about our protocol: a) the test failure criteria and b) confirmation that we will specifically instruct seniors to use only the scissors provided during the tests. To that end, please find attached a summary document addressing Dr. Gross' questions, including information especially on the toxic dose calculations, total number of studies needed, and the test failure criteria proposed for the CRP testing of Advantage Plus/IGR blisters. The failure rates shown in the attached are the same as used in the previously conducted studies (Child test example: Bayer Report No. 75897; MRID 47089103 and Adult test example: Bayer Report No. 75898; MRID 47089104) that were used to support the currently registered Advantage Plus product/packages.

We request that this information be forwarded to Dr. Gross to answer her questions. We are planning to conduct these studies in mid-April, so if Dr. Gross has any questions or comments, we would appreciate her feedback as soon is it is available.

Sincerely,

Doug Spilker

Douglas A. Spilker, Ph.D. Manager - EPA Reg. Affairs BAYER HEALTHCARE LLC ANIMAL HEALTH

Office: +1 913-268-2751 Mobile: +1 816-506-3102 Fax: +1 913-268-2135

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Address: P.O. Box 390 Shawnee Mission, KS 66201-0390 Country: USA

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For alternate languages please go to http://bayerdisclaimer.bayerweb.com [attachment "Advantage IGR CRP Testing -For EPA Review 3-27-09.doc" deleted by Kable Davis/DC/USEPA/US]

Doug Spilker/SHAWN/AGCHEM/US /BAYER 03/30/2009 02:21 PM To davis.kable@epa.gov

cc Harish
Chopade/SHAWN/AGCHEM/US/BAYER@BAYER-US-NOT
ES

bcc Mary

Hunt/SHAWN/AGCHEM/US/BAYER@BAYER-US-NOTES;

Ciszewski/SHAWN/AGCHEM/US/BAYER@BAYER-US-NOT

ES; Bruce

Martin/SHAWN/AGCHEM/US/BAYER@BAYER-US-NOTES;

Douglas

Hutchens/SHAWN/AGCHEM/US/BAYER@BAYER-US-NOT

ES; Jagdeep

Buch/SHAWN/AGCHEM/US/BAYER@BAYER-US-NOTES
CRP Testing for Paying Reckaging of Advantage Rive

Subject CRP Testing for Revised Packaging of Advantage Plus

Products

Dear Mr. Davis,

Reference is made to the meeting of March 4, 2009 (BAH: D. Spilker; EPA: B. Davis, V. Eagle and R. Gross), which included a discussion on Advantage Plus for Dogs (11556-125, -127, -128, -130) and our plans to develop revised packaging for these products, as well as for the yet-to-be submitted Advantage IGR for Cats product. As you will recall, these products require child-resistant packaging. As we discussed, we understand that the full battery of tests with children and adult seniors, as well as with all package sizes (colors) and all package configurations (4-packs and 6-packs) is required. We will conduct these tests as before with Great Lakes Marketing Company, Toledo, Ohio.

In the aforementioned meeting, we discussed with Dr. Rosalind Gross the CRP Testing plans. In that conversation, Dr. Gross requested we send her some specific information about our protocol: a) the test failure criteria and b) confirmation that we will specifically instruct seniors to use only the scissors provided during the tests. To that end, please find attached a summary document addressing Dr. Gross' questions, including information especially on the toxic dose calculations, total number of studies needed, and the test failure criteria proposed for the CRP testing of Advantage Plus/IGR blisters. The failure rates shown in the attached are the same as used in the previously conducted studies (Child test example: Bayer Report No. 75897; MRID 47089103 and Adult test example: Bayer Report No. 75898; MRID 47089104) that were used to support the currently registered Advantage Plus product/packages.

We request that this information be forwarded to Dr. Gross to answer her questions. We are planning to conduct these studies in mid-April, so if Dr. Gross has any questions or comments, we would appreciate her feedback as soon is it is available.

Sincerely, Doug Spilker

Douglas A. Spilker, Ph.D. Manager - EPA Reg. Affairs BAYER HEALTHCARE LLC ANIMAL HEALTH

Office: +1 913-268-2751 Mobile: +1 816-506-3102 Fax: +1 913-268-2135

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Country: USA

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Advantage IGR CRP Testing -For EPA Review 3-27-09.doc

Child-Resistant Packaging and Toxicology of Advantage® IGR Formulation for Use in Cats and Dogs for Flea Control

INTRODUCTION

The packaging requirements for pesticides and devices to be marketed in the United States are prescribed in Code of Federal Regulations, 40 CFR Part 157.20. Bayer Animal Health has developed a new product, Advantage® IGR (previously known as Advantage® Plus), containing 9.1% imidacloprid and 0.46% pyriproxyfen as a spot-on formulation for dogs and cats for the control of fleas (all stages). The product will be marketed as three different sized tubes (1.0-mL, 2.5-mL and 4.0-mL total capacity) packaged in a 4-pack and 6-pack child resistant blisters. For cats, 0.23 mL, 0.4 mL or 0.8 mL product will be placed in a 1.0-mL capacity tube. For dogs, 0.4 mL or 1.0 mL product will be placed in a 1.0-mL tube, 2.5 mL product in a 2.5-mL tube, and 4.0 mL product in a 4.0-mL tube. The child-resistant (CR) feature of the packaging is the blisters. The tubes are not child-resistant; tubes will be identical to those currently marketed for Advantage® and K9 Advantix® products.

CALCULATION OF TOXIC DOSE

The acute oral LD₅₀ for this new product (formulation with 9.1% imidacloprid and 0.9% pyriproxyfen) was determined to be 1,283 mg/kg for male and 1,000 mg/kg for female rats. This product meets the US EPA 40 CFR Part 157.22 requirements for child-resistant packaging according to the following toxicity criteria: (1) Toxicity criterion – the pesticide has an oral LD₅₀ of 1.5 g/kg or less, and (2) Use criterion – The product's labeling either directly recommends residential use or reasonably can be interpreted to permit residential use.

In Table 1, below, are given the number of tubes of each different size of this product a child weighing 25 pounds (11.4 kg) would have to ingest to reach a toxic dose (amount). "Toxic dose" for this product as defined in 40 CFR Part 157.22 and that confirmed by Dr. Rosalind Gross of US EPA is the acute oral LD₅₀ value. Thus, to err on the conservative side, the LD₅₀ value of 1,000 mg/kg (= 1.0 g/kg) for female rats was used in the supporting calculations. The density of the product, 1.092 g/mL, was also used in the supporting calculations. A toxic dose of the Advantage® IGR formulation for a child (25 lb = 11.4 kg) is calculated as 10.44 mL of Advantage® IGR product [i.e., (1.0 g/kg LD₅₀x 11.4 kg body weight) \div (1.092 g/mL density) = 10.44 mL].

771-7.1-1 7	C-1 Of	MT	CT-L	Trans.	Cara Child a	
rabie i. i	lude Sizes.	, ivumber ()I 1 UDCS 45	TOXIC DOSE	TOF A CHUG. 2	nd Test Failure Criteria

Advantage® IGR	No. of Tubes* Constitute	Test Failure Criteria
Tube Size (mL)	as Toxic Dose for a Child	(# Tubes Accessed by a Child)
0.23	46 (45.4)	9**
0.4	27 (26.1)	9
0.8	13 (13.05)	9
1.0	11 (10.4)	9
2.5	5 (4.2)	5
4.0	3 (2.6)	3

^{*}Calculated tube number in the parenthesis (with ≥ 0.1 fraction) is rounded off to the next higher integer. All tubes are single use, which means each tube contents are used as a single application.

**Per EPA guidance, 9 tubes is recommended as the test failure criteria for child panel testing when ≥ 9 tubes represent a toxic dose for a child.

Reference: 1. Sturdivant, D.W. 1999. Acute oral LD₅₀ toxicity study with imidacloprid (9.1%)/pyriproxyfen (0.9%) spot-on in rats, Bayer Animal Health Report No. 75195, MRID No. 45096904.

CRP TESTING OF BLISTERS

Bayer is planning on testing Advantage® IGR blisters made with two different lidding foils: Tropical foil and PVC foil. As individual tube sizes of Advantage® IGR to be marketed for dog and cat will be colored differently, we are going to CRP test individual tube size and blister type (4-pack or 6-pack). Therefore, for blisters with either Tropical or PVC lidding foil, there will be a total of 8 CRP studies (8 child panel + 8 senior adult panel) for the dog product (Table 2) and 5 CRP studies (5 child panel + 5 senior adult panel) for the cat product (Table 3) for each lidding foil type blisters. As a guideline requirement for CRP testing purposes, all tubes will be filled with appropriate volume of water.

Table 2. Blister Packaging (CRP Studies) for Dogs

Tube Size* & Color Scheme	No. of Tubes Blister Type Toxic Dose to 25-lb Child		Test Failure Criteria to be Followed (Minimum # of Tubes Accessed by a Child)
0.4 mL	4 pack	27	9
Green (Pantone 346C)	6 pack	27	9
1.0 mL	4 pack	11	9
Turquoise (Pantone 311C)	6 pack	11	9
2.5 mL	4 pack	5	5
Red (Pantone 197C)	6 pack	5	. 5
4.0 mL Blue (Pantone 543C)	4 pack	3	3
	6 pack	3	3

^{*}Each tube will contain appropriate volume of water.

Table 3. Blister Packaging (CRP Studies) for Cats

Tube Size* & Color Scheme	Blister Type	No. of Tubes = Toxic Dose to a 25-lb Child	Test Failure Criteria to be Followed (Minimum # of Tubes Accessed by a Child)			
0.23 mL Turquoise (Pantone 326C)	4 pack	46	9			
0.4 mL	4 pack	27	9			
Orange (Pantone 157C)	6 pack	27	9			
0.8 mL Purple (Pantone 264C)	4 pack	13	9			
	6 pack	13	. 9			

^{*}Each tube will contain appropriate volume of water.

CONDUCT OF CRP STUDIES

Both child panel and senior adult panel CRP studies for each blister & tube size (water-filled) will be performed according to the test protocol prescribed in the Federal Register, Title 16, Part 1700.20, by Great Lakes Marketing, Toledo, Ohio. Data collected for the studies will be analyzed and reported according to the Agency guidelines. Also, CRP protocol test data will be made available to the Agency electronically on a CD-R.

A Tube Failure Criterion in Child Panel Testing: In child panel testing (50 to 200 participants), any small breach of a blister cavity (clearly visible small incision or opening) made by a child with finger nails or teeth would be counted as one tube failure.

<u>Use of a Pair of Scissors in Senior Adult Panel Testing</u>: A senior adult panel will include 100 participants. As the blister Opening Instructions involve the use of a pair of scissors, senior adult participants will be allowed to use a pair of scissors during the testing, but they will be warned against using a pocket knife or other tools.

Rayer Health Care Animal Health



Via Federal Express

February 2, 2010

Office of Pesticide Programs (7504P) – Request for CRP Determination (NO REG FEE)
U.S. Environmental Protection Agency
Room S-4900, One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202-4501

Attention: Ms. Venus Eagle (PM 01)

Registration Division

Subject: Advantage Plus products for dogs*

(EPA Reg. Nos. 11556-125, -127, -128, -130)

Advantage IGR products for cats*

(EPA File Symbols. 11556-RLN. -RLR, -RLE)

Request for Determination that Single Tubes of Products are Not Subject to CRP Requirements

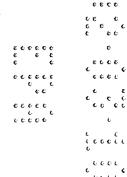
Dear Ms. Eagle:

Reference is made to a teleconference, intiated by the Agency, between Bayer Healthcare, Animal Health Division (D.A. Spilker/H. Chopade) and Ms. Rosalind Gross of the Agency (January 13, 2010) regarding the currently under-review Child-Resistant Packaging studies, submitted for the pending actions of Advantage Plus for Dogs and Advantage IGR (for cats.) In addition to other topics, there was discussion on the possibility of receiving a determination from the Agency that "single tube" presentations of the subject products (all containing the identical formulation) would not be subject to the requirement of Child-Resistant Packaging. In addition to marketing 4- and 6-packs of the products (in CRP packaging), Bayer plans to market all of the products in single tube presentations.

*The following table lists all of the products and actions involved with this request:

Animal Health P.O. Box 390 Shawnee Mission, KS 66201-0390

Bayer HealthCare LLC



Ms. Venus Eagle Registration Division Office of Pesticide Programs (7504P) U.S. Environmental Protection Agency Page 2 February 2, 2010

Product	Reg/File Symbol No.	Decision Number
Advantage Plus 20 for Dogs	11556-125	D-424617
Advantage Plus 55 for Dogs	11556-127	D-424616
Advantage Plus 10 for Dogs	11556-128	D-424618
Advantage Plus 100 for Dogs	11556-130	D-424615
Advantage IGR 18 (for Cats)	11556-RLE	D-424199
Advantage IGR 9 (for Cats)	11556-RLR	D-424200
Advantage IGR 5 (for Cats)	11556-RLN	D-424201

Based on the toxic dose calculations presented in the attached document, it becomes evident that a single tube of any of the 7 different sizes (or 0.23 mL to 4.0 mL formulation) would not approach an acutely toxic dose for a child weighing 25 lb. Therefore, child-resistant packaging for the single-tube packaging for Advantage® IGR/Plus products for dogs and cats should not be required nor should there be any need for CRP testing in this case. Therefore, as recommended by Ms. Gross in the aforementioned teleconference, we request the Agency to make a determination that single tube presentations of the aforementioned products are not subject to the CRP requirements.

If you have any questions, please do not hesitate to call me at (913) 268-2751.

Sincerely

Douglas A. Spilker. Ph. D.

Manager, EPA Regulatory Affairs

Doug.Spilker.b@Bayer.com

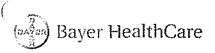
DAS

Attachment:

 "A Request for Determination That Single Tube packaging of Advanatge IGR/Plus Products are Not Subject to CRP Requirements," dated 02/01/10, 3pp.

Cc::

Kable Davis, EPA Autumn Metzger, EPA Rosalind Gross, EPA



A Request for a Determination That Single-Tube Packaging of Advantage® IGR/Plus Products Are Not Subject to CRP Requirements

1. OBJECTIVE

Bayer HealthCare, Animal Health Division, Shawnee, Kansas, is requesting a determination by EPA that <u>single-tube</u> packaging of Advantage® IGR/Plus products (containing an identical formulation), for use on cats and dogs for flea control, are not subject to CRP requirements. The background information on the Advantage® IGR/Plus packaging and the justification for support of this proposed determination are presented below.

2. INTRODUCTION

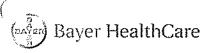
Bayer has developed a new product, Advantage® IGR (previously known as Advantage® Plus), containing 9.1% imidacloprid and 0.46% pyriproxyfen as a spot-on formulation for dogs and cats for the control of fleas (all stages); see Table 1 below for respective registration/file symbol numbers. Bayer's plan is to market the product for use on dogs as four different sized tubes (0.4-mL, 1.0-mL, 2.5-mL, and 4.0-mL capacity) packaged in 4-pack and 6-pack child-resistant blisters. For cats, three different volumes will be marketed, 0.23-mL, 0.4-mL or 0.8-mL; 0.4-mL and 0.8-mL tubes will be placed in 4-pack and 6-pack blisters, but the 0.23-mL tubes will be packaged in 4-pack blister only. The child-resistant (CR) feature of the product packaging is the 4-pack and 6-pack blisters. The plastic tubes are not child-resistant. Moreover, the tubes will be distinctly color-coded by sizes. For the marketing of the Advantage® IGR 4-pack and 6-pack KISI blisters, Bayer HealthCare sought advice and concurrence from Dr. Rosalind Gross of USEPA (1Q 2009), and subsequently completed the CRP testing for the 4-pack and 6-pack KISI blisters. These blisters passed the CRP testing, and the final reports for both cat and dog products were submitted to EPA for review in November 2009.

3. SINGLE-TUBE PACKAGING FOR ADVANTAGE® IGR PRODUCTS FOR CATS AND DOGS

Now, Bayer has decided to additionally market all Advantage® IGR products in single-tube packaging. We are proposing three single-tube packages (three color-coded tube types) for cats (0.23-mL, 0.4-mL, and 0.8-mL) and four single-tube packages (four color-coded tube types) for dogs (0.4-mL, 1.0-mL, 2.5-mL and 4.0-mL).

Tube Size & Color Scheme for Cats	Tube Size & Color Scheme for Dogs	
0.23 mL (Turquoise; Pantone 326C) (EPA File Symbol 11556-RLN)	0.4 mL (Green; Pantone 346C) (EPA Reg. No. 11556-128)	. c .
0.4 mL (Orange; Pantone 157C) (11556-RLR)	1.0 mL (Turquoise; Pantone 311C) (11556-125)	6 C
0.8 mL (Purple; Pantone 264C) (11556-RLE)	2.5 mL (Red; Pantone 2976) (11556-127)	¢ 6
	4.0 mL (Blue; Pantone 545C) (11556-130)	٠,

Table 1. Single-Tube Packaging for Cats and Dogs



4. CALCULATION OF TOXIC DOSE

The acute oral LD_{50} for this new product (M880 Insecticide formulation containing 9.0% imidacloprid and 0.48% pyriproxyfen) was determined to be 1,098 mg/kg for female rats.¹ This product meets the US EPA 40 CFR Part 157.22 requirements for child-resistant packaging according to the following toxicity criteria: (1) Toxicity criterion – the pesticide has an oral LD_{50} of 1.5 g/kg or less, and (2) Use criterion – The product's labeling either directly recommends residential use or reasonably can be interpreted to permit residential use.

In Table 2, below, are given the number of tubes of each different size of this product a child weighing 25 pounds (11.4 kg) would have to ingest to reach a toxic dose (amount). "Toxic dose" for this product as defined in 40 CFR Part 157.22 and that confirmed by Dr. Rosalind Gross of US EPA is the acute oral LD₅₀ value. The LD₅₀ value of 1,098 mg/kg (= 1.098 g/kg) for female rats was used in the supporting calculations. The density of the product, 1.092 g/mL, was also used in the supporting calculations. A toxic dose of the Advantage® IGR formulation for a child (25 lb = 11.4 kg) is calculated as 11.46 mL of Advantage® IGR product [i.e., (1.098 g/kg LD₅₀ x 11.4 kg body weight) \div (1.092 g/mL density) = 11.46 mL].

Table 2. Tube Sizes, Number of Tubes as Toxic Dose for a Child, and Test Failure Criteria

Advantage® IGR Tube Size (mL)	No. of Tubes* Constitute as Toxic Dose for a Child	Test Failure Criteria (# Tubes Accessed by a Child)
0.23	50 (49.9)	9**
0.4	29 (28.7)	9
0.8	I5 (14.4)	9
1.0	I2 (11.5)	9
2.5	5 (4.6)	5
4.0	3 (2.9)	3

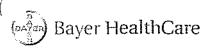
^{*}Number in the parenthesis is rounded off to the next higher integer. All tubes are single use only, which means each tube contents are used as a single application.

5. REQUEST FOR A WAIVER OF THE REQUIREMENT FOR CRP PACKAGING OF SINGLE-TUBE PRODUCTS

Based on the toxic dose calculations presented above, 11.46 mL of the formulation of Advantage® IGR represents a "toxic dose" for a 25-lb child. Therefore, after evaluating the toxicity of the single-tube packaging proposed above, it became clearly evident that a single tube of any of the 7 different sizes (or 0.23 mL to 4.0 mL formulation) would not approach an acutely toxic dose for a child weighing 25 lb. Therefore, single-tubes for Advantage® IGR products for cats and dogs need not be placed in child-resistant packaging (GRP) nor should there be any need for CRP testing of these presentations. However, based on the advice from Dr. Rosalind Gross of the EPA to Bayer Representatives (Drs. Doug Spilker and Harish Chopade; telephone communication 1/13/10), this single-tube packaging would need to be distinctly different in appearance from the CRP 4-pack and 6-pack KISI blisters mentioned above.

^{**}Per EPA guidance, accessing a minimum of 9 lubes are recommended as the test failure criteria for child panel testing when ≥ 9 tubes represent a loxic dose for a child.

 $^{^1}$ MRtD No. 47089411, "An Acute Oral LD₅₀ Study in the Rat with M880 Insecticide," EPA Guideline No. 870.110b, Bayer Report No. 75922 (ID No. 23792), D. A. Eigenberg, 2007, 34 p.

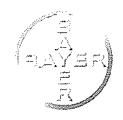


CONCLUSION

Bayer Healthcare, Animal Health Division, is requesting EPA to make the determination that single-tube presentations of all the aforementioned Advantage® IGR/Plus products (containing an identical formulation) are not subject to CRP requirements based on the justification given above. Furthermore, if the requested determination is made, we acknowledge and agree to the condition for making the single-tube packaging distinctly different from the CRP 4-pack and 6-pack KISI blisters that are currently under review at the Agency, on the advice from Dr. Rosalind Gross of the EPA.

BAYEL DOG STUDY ID Applies to Add

Bayer **HealthCare**Animal Health



Via Federal Express

February 1, 2010

Office of Pesticide Programs (7504P) – Additional Data (NO REG FEE)
U.S. Environmental Protection Agency
Room S-4900, One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202-4501

Attention: Ms. Rosalind Gross (Child-resistant Packaging)

Registration Division

Subject: Advantage Plus products for dogs

(EPA Reg. Nos. 11556-125, -127, -128, -130)

Submission of Additional Copies of Raw Data from previously

submitted CRP reports

Dear Ms. Gross:

Reference is made to the your telephone request of Bayer Healthcare, Animal Health Division (R. Gross to D.A. Spilker/ H. Chopade, January 13, 2010) regarding the need for resubmission of the raw data from the Child-Resistant packaging studies submitted for the pending actions (dated 12/7/2009) for Advantage Plus 10 for Dogs (EPA Reg. No. 11556-128), Advantage Plus 20 for dogs (11556-125), Advantage Plus 55 for Dogs (11556-127) and Advantage Plus 100 for Dogs (11556-130).

(11550-127) and Advantage 1 tag 100 for Dogo (11550 150).

As requested, please find enclosed two identical copies (CDs) of the requested data. A contents list of the files included is also enclosed.

If you have any questions, please do not hesitate to call me at (913) 268-2751.

Bayer HealthCare LLC Animal Health P.O. Box 390 Shawnee Mission, KS 66201-0390 Bayer Healthcare, Animal Health Division P.O. Box 390 Shawnee Mission, KS 66201

Contents of CDs:

To identical additional copies of the raw data files from previously submitted CRP reports - Bayer Report Nos. 33717 - 33732 (see attached EPA correspondence).

In support of pending actions for Advantage Plus for Dogs (EPA Reg. Nos. 11556-125, -127, -128 and -130).



Das 02/01/2010

Transmittal Document

1. <u>Name and Address of Submitter</u>

Bayer HealthCare LLC Animal Health Division

Box 390

Shawnee Mission, Kansas 66201-0390

Douglas A. Spilker, Ph.D.

Manager, EPA Regulatory Affairs

Volume

(913) 268-2751

2. Regulatory Action in Which this Package is Submitted

Data submitted to support revised label claim for Advantage® Plus 100 for Dogs (EPA Reg. No. 11556-130)

3. Transmittal Date

MRID No.

December 7, 2009

4. <u>List of Submitted Studies</u>:

47932001	1	-	"Child-Resistant Packaging (CRP) Child Panel Test of
			4 x 4.0 mL Advantage® IGR KISI Blisters for Dogs,"
			40 CFR Part 157.20 and 16 CFR Part 1700.20,

L. M. Dixon, Report No. 33717, 54 p.

47932002 2 - "Child-Resistant Packaging (CRP) Senior Adult Panel

Test of 4 x 4.0 mL Advantage® IGR KISI Blisters for Dogs," 40 CFR Part 157.20 and 16 CFR Part 1700.20,

L. M. Dixon, Report No. 33718, 250 p.

47932003 3 - "Child-Resistant Packaging (CRP) Child Panel Test of

6 x 4.0 mL Advantage® IGR KISI Blisters for Dogs," 40 CFR Part 157.20 and 16 CFR Part 1700.20,

L. M. Dixon, Report No. 33719, 56 p.

47932004 4 - "Child-Resistant Packaging (CRP) Senior Adult Panel

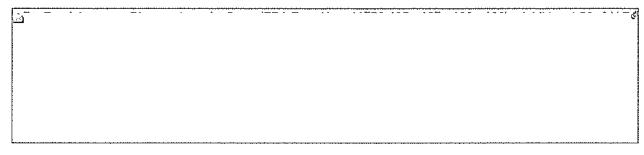
Test of 6 x 4.0 mL Advantage® IGR KISI Blisters for Dogs," 40 CFR Part 157.20 and 16 CFR Part 1700.20,

L. M. Dixon, Report No. 33720, 246 p.

Fw: Advantage Plus products for Dogs (EPA Reg. Nos. 11556-125, -127, -128, -130) - Additional CRP Info

Rosalind Gross to: Autumn Metzger

01/14/2010 04:48 PM



Could you please place a copy of this email and the attachment in the file jacket for EPA Reg. Nos. 11556-125, -127, -128, -130. Thanks.

Rosalind Gross
Registration Division
One Potomac Yard
Mail Code 7505P
2777 S. Crystal Drive
Arlington, VA 22202
telephone 703-308-7368
fax 703-308-9382
cube7338
email gross.rosalind@epa.gov

---- Forwarded by Rosalind Gross/DC/USEPA/US on 01/14/2010 04:46 PM -----



Advantage Plus products for Dogs (EPA Reg. Nos. 11556-125, -127, -128, -130) - Additional CRP Info

Doug Spilker to: Rosalind Gross

01/14/2010 04:10 PM

Cc: Kable Davis, Autumn Metzger, Harish Chopade

Dear Ms. Gross,

Reference is made to our telephone discussion yesterday, January 13, 2010, regarding the Child Resistant Packaging (CRP) testing as it relates to the subject products for dogs. In the aforementioned discussion, with our Dr. Chopade and me, you requested the submission of some additional clarifying information regarding the CRP testing with children and senior adults that we submitted on December 11, 2009 to revise the packaging and respective use directions for these products.

Please find attached a chart, as you requested, that cross references the study numbers, MRID numbers and EPA registration numbers, with additional information including:

- a) further detail, in addition to what is in the reports, as to what constituted a failure in both the child and adult tests, and
- b) further clarification as to the exact number of cards (blister packs) given in each of the trials.

We understand that the information presented in this form is adequate for your use, and will become a part of the official file for review. If you need anything further, please do not hesitate to call.

Best regards, Doug

Douglas A. Spilker, Ph.D. Manager - EPA Reg. Affairs BAYER HEALTHCARE LLC ANIMAL HEALTH Office: +1 913-268-2751

Office: +1 913-268-2751 Mobile: +1 816-506-3102 Fax: +1 913-268-2135

Email: doug.spilker.b@bayer.com

Address: P.O. Box 390 Shawnee Mission, KS 66201-0390 Country: USA

Bayer Animal Health "Protecting.Curing.Caring...Together"

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For alternate languages please go to http://bayerdisclaimer.bayerweb.com

Advantage IGR Dog - CRP Info 1-14-10.pdf

PRIA 2 – 21 Day Content Screen Review Worksheet (EPA/OPP Use Only) 3/23/09

Expe	ay Screen Start Date:	<u>5</u> -09 ate	Fee F	aid: Yo	es <u>V</u>	
EPA I	Reg. Number: 11556-128 EPA Receipt Date: 1	2-11	-09			
	Items for Review			Yes	No	N/A*
1	Application Form (EPA Form 8570-1)(link to form) signed & co including package type	· ·····	×			
2	Confidential Statement of Formula all boxes completed, form side dated (EPA Form 8570-4) (Link to form)		nd			×
	a) All inerts (link to http://www.epa.gov/opprd001/inerts/), including fragrances, approved for the proposed uses (see Footnote A)	yes	no	,		
3	Certification with Respect to Citation of Data (EPA Form 8570 form) completed and signed (N/A if 100% repack)	ink to	X			
	Certificate and data matrix consistent	X				
	If applicant is relying on data that are compensable, is the offer to pay statement included. (see Footnote B)					
	If applicable, is there a letter of Authorization for exclusive use or	ıly.				
4	Formulator's Exemption Statement (EPA Form 8570-27) (Link completed and signed (N/A if source is unregistered or applicant of technical)				X	
	Data Matrix (EPA Form 8570-35) (Link to form) both internal arcopies (PR 98-5) (Link to PR 98-5) completed and signed (N/A if repack)	nal	X			
5	a) Selective Method (Fee category experts use)	yes	no			
	b) Cite-All (Fee category experts use)					
	c) Applicant owns all data (Fee category experts use)					
6	5 Copies of Label (link to http://www.epa.gov/oppfead1/labeling (Electronic labels on CD are encouraged and guidance is available http://www.epa.gov/pesticides/regulating/registering/submissions/index.	able)(l	ink to	X		

7	Is the data package consistent with PR Notice 86-5 (link to PRN 86-5)	X	
8	Notice of Filing (link to http://www.epa.gov/pesticides/regulating/tolerance_petitions.htm) included with petitions (link to http://www.epa.gov/pesticides/regulating/tolerances.htm)		\rightarrow
9	If applicable for conventional applications, reduced risk rationale (link to http://www.epa.gov/opprd001/workplan/reducedrisk.html)		×
	Required Data (link to http://www.epa.gov/pesticides/regulating/data_requirements.htm) and/or data waivers. See Footnote C. a) List study (or studies) not included with application		
10			

Comments:

CERTIFICATION FORM WAS MISSING. REGISTRANT WAS CONTACTED, AND SUPPLIED THE FORM ON 12/18/09. AA 12/22/09

MRID 479323

* N/A – Not Applicable

Footnotes

A. During the 21 day initial content review, all CSFs will be reviewed to determine whether all inerts listed, including fragrances, are approved for the proposed uses. If an unapproved inert is identified, the applicant must either 1) resolve the inert issue by, for example, removing the inert, substituting it with an approved inert, submitting documentation that EPA approved the inert for the proposed pesticidal uses, correcting mistakes on the CSF, etc. or 2) provide the data to support OPP approval of the inert or 3) withdraw the application. Removing or substituting an inert ingredient will require a new CSF and may require submission of data. All information, forms, data and documentation resolving the inert issue must have been received by the Agency or the application withdrawn within the 21 day period, otherwise, the Agency will reject the application as described below.

To successfully complete this aspect of the 21 day initial content screen, applicants are strongly encouraged to verify that all inert ingredients have been approved for the application's uses even if a product is currently registered by consulting the inert Web

site [link to http://www.epa.gov/opprd001/inerts/lists.html] and if the inert is not approved, to obtain the necessary inert approval prior to submitting an application to register a pesticide product containing that inert ingredient. Some inert ingredients are no longer approved for food uses or certain types of uses. The name and/or CAS number on a CSF must match the name and CAS number on this web site. Simple typographical errors in the name or CAS number have resulted in processing delays.

If an inert is not listed on the inert ingredient web site and the applicant believes that the inert has been approved, the applicant should contact the Inert Ingredient Assessment Branch (IIAB) at inertsbranch@epa.gov and resolve the issue. Copies of the correspondence with IIAB resolving the issue should accompany the application. All new inerts except PIP inerts are reviewed by IIAB. The IIAB should also be contacted for any questions on what supporting data needs to be submitted for and the Agency's inert review process. Questions on PIP inerts should be directed to the Chief of Microbial Pesticides Branch [Link to http://www.epa.gov/oppbppd1/biopesticides/contacts bppd.htm].

When a brand, trade, or proprietary name of an inert ingredient is listed on a CSF, additional information such as an alternate name of the inert, CAS number or other information [link to http://www.epa.gov/opprd001/inerts/tips.pdf] must also be included to enable the Agency to determine if it has been approved. Each component of an inert mixture (including a fragrance) must be identified. In some cases, the supplier of the mixture or fragrance may need to provide this information to the Agency. Prior to the Agency's receipt of an application, applicants must arrange with a proprietary mixture or fragrance supplier to provide the component information to the Agency or promptly upon EPA's request. If the inert ingredients in a proprietary blend (including fragrances) cannot or are not identified or provided within the 21-day content review period, the Agency will reject the application.

During the 21 day content review, applicants should submit information to the individual identified by the Agency when the applicant is informed of an unapproved inert.

Unapproved Inerts Identified on CSFs

All applications except conventional new products and PIPs

Once an unapproved inert is identified on a CSF, the Agency will contact the applicant with the following options:

- 1. Correct the application by, for instance, correcting the inert's identity or CAS number, providing documentation that the inert has been approved, or removing the unapproved inert from the CSF or replacing it with one that is approved for the application's uses; or
- Submit the information and data needed for the Agency to approve the unapproved inert. If this option is selected and implemented, the Agency may request an extension in the PRIA decision review timeframe to accommodate the inert review/approval process;

3. Withdraw the application (the Agency retains 25% of the full fee for the fee category estimated); or

If none of these options is selected and implemented by the applicant within the 21 day content review period, the Agency will reject the application and retain 25% of the full fee of the category identified.

Conventional New Product Applications

When the Registration Division identifies an unapproved inert on a CSF with an application for a new product that the applicant has not identified as requiring an inert approval (R311, R312 or R313), it will contact the applicant with the following options:

- 1. Correct the application by, for instance, correcting the inert's identity or CAS number, providing documentation that the inert has been approved, or removing the unapproved inert from the CSF or replacing it with one that is approved for the application's uses; or
- 2. Submit the information and data needed for the Agency to approve the unapproved inert, including any required petition to establish or amend a tolerance or exemption from a tolerance. (This option may change the PRIA category for the application, which could require a longer decision review time and a larger fee. If additional fees are due, they must be received by the Agency within the 21 day content review period.)
- 3. Withdraw the application (the Agency retains 25% of the full fee for the fee category estimated); or

If none of the above options is selected and implemented during the 21-day content-review period, the Agency will reject the application and retain 25% of the appropriate fee for the new product-inert approval category.

PIP Applications

When the Biopesticide and Pollution Prevention Division identifies an unapproved inert on a PIP CSF and a request to approve the inert does not accompany the application, it will contact the applicant with the following options:

- Correct the application by, for instance, correcting the spelling or name of the inert to that in 40 CFR 174, or providing documentation that the inert has been approved; or
- 2. Submit the information and data needed for the Agency to approve the unapproved inert. If an inert ingredient tolerance exemption petition is required, the petition must be received by the Agency and the B903 fee paid within the 21 day period. If this option is selected and implemented, the Agency will discuss harmonizing the timeframe for both actions.

3. Withdraw the application (the Agency retains 25% of the full fee for the fee category estimated); or

If none of the above options is selected and implemented during the 21 day content review period, the Agency will reject the application and retain 25% of the fee.

- B. A policy on documentation of offers to pay is still being developed, however, for a me-too or fast track (similar/identical) new product, R300 or A530, an application without the necessary authorizations of offers to pay will be placed into either R301 or A531. The Agency recommends that authorizations of offers to pay be submitted with other PRIA applications to avoid delays in the Agency's decision.
- C. Biopesticide applicants are advised to contact the Agency and discuss study waivers prior to submitting their application to the Agency. Documentation of such discussions should be submitted with the study waiver.



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY WASHINGTON, D.C. 20460

December 17, 2009

OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

BAYER HEALTHCARE LLC ANIMAL HEALTH DIVISION PO Box 390 SHAWNEE MISSION, KS 66201-0390

Report of Analysis for Compliance with PR Notice 86-5

Thank you for your submittal of 11-DEC-09. Our staff has completed a preliminary analysis of the material. The results are provided as follows:

Your submittal was found to be in full compliance with the standards for submission of data contained in PR Notice 86-5. A copy of your bibliography is enclosed, annotated with Master Record ID's (MRIDs) assigned to each document submitted. Please use these numbers in all future references to these documents. Thank you for your cooperation. If you have any questions concerning this data submission, please raise them with the cognizant Product Manager, to whom the data have been released.



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY WASHINGTON, D.C. 20460

December 15, 2009

OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

OPP Decision Number: D-424618

EPA File Symbol or Registration Number: 11556-128

Product Name: Advantage Plus 10 for Dogs

EPA Receipt Date: 11-Dec-2009 EPA Company Number: 11556

Company Name: BAYER HEALTHCARE LLC

DOUGLAS A. SPILKER, PH.D. BAYER HEALTHCARE LLC ANIMAL HEALTH DIVISION PO Box 390 SHAWNEE MISSION, KS 66201-0390

SUBJECT: Receipt of Registration Amendment Subject to Registration Service Fee

Dear Registrant:

The Office of Pesticide Programs has received your amendment and certification of payment. If you submitted data with this application, the results of the PRN-86-5 screen will be communicated separately. During the administrative screen, the Office of Pesticide Programs has determined that this Action is subject to a Pesticide Registration Service Fee as defined in the Pesticide Registration Improvement Act.

The Action has been identified as Action Code: R340

NON-FAST-TRACK (INCLUDES CHANGES TO PRECAUTIONARY LABEL STATEMENTS; SOURCE CHANGES TO AN UNREGISTERED SOURCE);

No additional payment is due at this time.

If you have any questions, please contact the Pesticide Registration Service Fee Ombudsman at (703) 305-6249.

Sincerely,

TIMERO

Front End Processing Staff

Information Technology & Resources Management Division

Fee for Service



This package includes the following	for Division					
○ New Registration	OAD					
Amendment	○BPPD ○RD					
☑ Studies? ☐ Fee Waiver?						
□ volpay % Reduction:	Risk Mgr. 1					
Receipt No. S-	863995					
EPA File Symbol/Reg. No.	11556-128					
Pin-Punch Date:	12/11/2009					
☐ This item is NOT subject to FFS action.						
Action Code:	Parent/Child Decisions:					
Requested: R340						
Granted: R340						
Amount Due: \$ <u>3,444</u> .						
Inert Cleared for Intended Use Uncleared Inert in Produc						
Reviewer: A C & S	Date: 12-15-09					
Remarks:						

Online Payment

Advantage Plus 10 for Dogs

Online Payment

Step 3: Confirm Payment

1 | 2 | 3

* #

Thank you.

Your transaction has been successfully completed.

Pay.gov Tracking Information

Application Name: PRIA Service Fees Pay.gov Tracking ID: 2502SONG Agency Tracking ID: 74091225841

Transaction Date and Time: 12/02/2009 15:07 EST

Payment Summary

Address Information

Account Douglas A. Spilker Holder Name:

Billing 12707 Shawnee Address: Mission Parkway

Billing Bayer Animal Address 2: Health

City: Shawnee

State / KS Province:

Zip / Postal 66216-1846

Country: USA

Account Information

Card Type: Master Card

Card Number: **********0576

Decision Number:

Registration 128 Numbers

Company Bayer HealthCare

Name: LLC, AH

Company 11556 Number:

Action Code: R340

Payment Information

Payment Amount: \$3,444.00 Transaction Date 12/02/2009

and Time: 15:07 EST

Please read instructions on reverse before	Completing form.	Form App	(<u>roved. QMB No. 20</u>	Print Form
SEPA Environ	United States mental Protection A Washington, DC 20460	gency	Registrat X Amendm Other	į
	Application for	or Pesticide - Sec	tion I	
1. Company/Product Number 11556-128		2. EPA Product Man Venus Eagle	nager	3. Proposed Clessification
4. Company/Product (Name) Advantage Plus 10 for Dogs		PM# 01		X None Restricted
5. Name and Address of Applicant Unclude 8 ayer HealthCare LLC, Animal Health P.O. 8 ox 390 Shawnee Mission, KS 66201-0390 Chack if this is a new address.	n Division	(b)(i), my product to:	is similar or identi	ice with FIFRA Section 3(c)(3) cal in composition and labeling
		ection - II		
X Amendment - Explain below. Resubmission in response to Ager Notification - Explain below.	ncy letter deted	Agency let	ed labels in response iter deted Application. Diain below.	to
Explanation: Use additional page of if Application for amendment of currer only; CRP packaging studies. Fee cate (Pay.gov Tracking ID 2502SONG; Age	nt product registration; Pro egory recommended by V	pposed Fee Category: R Eagle (PM01). See atta	chment (4pp.) for i	more information.
	S	ection - III		
1. Material This Product Will Be Peckage	d In:			
Child-Resistant Peckaging X Yes* No No Certification must be submitted Unit Peckaging Ves X No If "Yes* Unit Packaging	No. per If	yes No. per ckege wgt centalne	2. Type of C	Container Metal Plactic Glese Peper Other (Specify)
3. Location of Nat Contants Information	4. Size(s) Reteil Co	ntainer	5. Location of Labe	ol Directions
Label Container 6. Manner in Which Label is Affixed to President		X Othe	See attachment	ng accempenying product
		ection - IV		
1. Contect Point	y below for identification of a	ndividual To be contacted,	, if necessary, to pro	cass this application.[
Nome Douglas A. Spilker, Ph.D.	Titla Mar	ager, EPA Reg. Affairs		Telephone No. (Include Area Code) 913-268-275ဦ ိ ေႏွစ
i cartify that the statements I have I acknowledge that eny knowingly both under epplicable law.	false or misleading statemer	t mey be punishebia by fi	ne or imprisonment i	(Stamped)
4. Typed Name Douglas A. Spilker, Ph.D.	Sclu Mar	ager, EPA Reg. Affairs 7 Dec 2	2009	(

Bayer HealthCare, Animal Health Division Advantage Plus 10 for Dogs EPA Reg. No. 11556-128 December 7, 2009

Attachment to: OPP APPLICATION FOR PESTICIDE – AMENDMENT

Section II – Explanation:

Bayer HealthCare, Animal Health Division, is proposing to revise the claims on the labels of Advantage Plus 10 for Dogs (EPA Reg. No. 11556-128) to revise the opening instructions and make minor label updates and modifications both desired by Bayer and recommended or permitted by the Agency. As the Agency's files will show, because the acute oral toxicity value for the product formulation was below the 1500 mg/kg "trigger," and because this is a residential use, the products must be marketed in Child-Resistant Packaging (CRP). We currently have acceptable CRP packaging data on file with the Agency (and the respective CRP Certification letters), but it is our desire to replace the current packaging with a different CRP packaging material. We chose to revise the opening instructions at the same time. These new opening instructions were used in the enclosed CRP testing studies (Bayer Reports 33729, 33730, 33731, and 33732). The respective studies being submitted for review, and all other reports being cited to support this registration are itemized in the enclosed Data Matrix, dated December 7, 2009.

Enclosed for the Agency's acceptance are five (5) copies of the revised draft labels, dated December 7, 2009, for Advantage Plus 10 for Dogs, EPA Reg. No. 11556-128. Enclosed is an identical copy of the aforementioned draft label, with the respective revisions highlighted for the Agency's convenience. The enclosed draft labeling has been revised from previous draft labeling versions to remove redundancy, but has the identical text as accepted by the Agency on September 18, 2007 (date of draft 9/17/2007; see Appendix 1), with the following changes:

A. General Format:

- 1) The label has been reformatted and consolidated to reduce redundancy.
- 2) The marketing claims have been moved from the front (pages 1 and 2) to pages 6 and 7 of draft labeling.

B. <u>Page 1:</u>

- 1) Addition of the word "weighing" in front of weight limitation in product description.
- 2) Addition of EPA Registration No. and Establishment No.
- 3) Deletion of the CAS numbers from the listing of active ingredients in the ingredient statement. As described on Page 5-3 of the Label. Review Manual, EPA will permit the use of common granges for each ingredient; the current label reflects this guidance. However, the inclusion of the CAS number on the label is rouly! an EPA recommendation, and due to space considerations on the final printed. labeling, we prefer the CAS numbers not be included on this label.
- 4) Addition of phrase "See back panel for First Aid."

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Bayer Health Care, Animal Health Division Advantage Plus 10 for Dogs EPA Reg. No. 11556-128 December 7, 2009

C. Page 2:

1) Addition of the first sentence under "First Aid" stating: "Have the product container or label with you when calling a poison control center or doctor, or going for treatment."

D. <u>Page 3:</u>

 Replacement of the entire "HOW TO OPEN" section with new opening directions. As the Agency will recall, because the acute oral toxicity value for the formulation was below the 1500 mg/kg "trigger," and because this is a residential use, the products must be marketed in Child-Resistant Packaging (CRP). These new opening instructions were used in the enclosed new CRP testing studies (Bayer Reports 33729, 33730, 33731, and 33732).

For the previous products, the CRP packaging was made of PVC and the respective child and adult testing data were found acceptable to the Agency. The proposed products will be produced in KISI blisters. The packaging material scheme for the proposed registrations is similar, and the CRP testing data for the various sizes are enclosed. The testing design to satisfy the requirements for all product presentations was developed with the agreement of the Agency's expert, Dr. Rosalind Gross (see Appendix 2). A CRP certification letter is also enclosed.

With regard to the overall CRP testing of the various packaging configurations, Bayer is aware of PR Notice 97-9 regarding the electronic submission of CRP test data, and therefore these data have been prepared appropriately and are included on a CD.

2) Removal of the graphics from the draft labeling that depicts how to open the applicator tube and graphics depicting application to the animal. A placeholder statement appears in both spots instead, to indicate that these graphics will appear on the final printed labeling. According to the Label Review Manual (16-1) "Graphics or symbols in addition to written text are permitted on pesticide product labels if they are accompanied by explanatory text..." We currently have EPA-accepted explanatory text that appropriately describes these processes. We intend to include the respective graphics on the final printed labeling, but request this change to allow flexibility in our ability to update the graphics in subsequent printings. We will follow all Agency guidelines on this subject, as outlined in the Label Review Manual, and will submit Final Printed Labeling with these graphics as new product is produced.

Bayer HealthCare, Animal Health Division Advantage Plus 10 for Dogs EPA Reg. No. 11556-128 December 7, 2009

3) Revision of third sentence of bullet 6:

<u>From:</u> "Place the tip of tube on the skin and squeeze the tube *twice* to expel the entire contents of the tube directly on the skin."

<u>To:</u> "Place the tip of tube on the skin and squeeze the tube to expel the entire contents of the tube directly on the skin."

It is our contention that the user should determine the number of times necessary to expel the entire contents of the tube.

E. Page 4:

- 1) Addition of sub-heading entitled "GENERAL INFORMATION."
- 2) As instructed by the Agency for our other spot-on products, the retreatment instructions were moved from the GENERAL INFORMATION section (see previous label draft, page 9 of 10) to the more appropriate "HOW TO APPLY" section, and appear as bullet No. 8. This bulleted section also has the new introductory statement "Under normal conditions the product is effective for a month."
- 3) Addition of the phrase "flea bite hypersensitivity" which is synonymous with "flea allergy dermatitis," a claim already accepted by the Agency.
- 4) As instructed by the Agency for our other spot-on products, revision of label text (paragraph 2 under "GENERAL INFORMATION") to remove the "98-100%" figure and change word "pet" to read "dogs."
- 5) Addition of a statement under "GENERAL INFORMATION" referring to lice control. This is not a new claim, we are just incorporating additional explanatory language about the pest in the text portion of the label. This claim previously only appeared in the marketing claims area of the label.
- 6) In sixth (6th) paragraph under GENERAL INFORMATION, change word "efficacious" to the synonym "effective."
- Revision of "STORAGE AND DISPOSAL" section according to PR Notice 2007-4.

F. Page 5:

 Revision of the address block to include a more complete registrant address; revision based on guidance from EPA Website – "Pesticide Label Question & Answers, No. 14; Name & Address Issues." Bayer HealthCare, Animal Health Division Advantage Plus 10 for Dogs EPA Reg. No. 11556-128 December 7, 2009

G. Page 6 - OPTIONAL MARKETING CLAIMS:

- Removal of the bulleted statement that reads "Available only through licensed practicing veterinarians" to make the packaging more accurate as to how our products are distributed.
- 2) As instructed by the Agency for our other spot-on products, removal of the "Canine Vector Borne Disease" claim and "% control" figure.
- 3) Minor word revision of currently accepted claims and inclusion of additional ways of describing the effectiveness and pesticidal properties of the product. See highlighted areas of the draft label.

Bayer HealthCare Animal Health



Via Federal Express

December 7, 2009

Document Processing Desk (REGFEE) Office of Pesticide Programs (7504P) U.S. Environmental Protection Agency Room S-4900, One Potomac Yard 2777 South Crystal Drive Arlington, VA 22202-4501

Attention: Ms. Venus Eagle

Registration Division

Subject: Applications for Amendment of the Registrations of:

Advantage[®]Plus 10 for Dogs (EPA Reg No. 11556-128) Advantage[®]Plus 20 for Dogs (EPA Reg. No. 11556-125) Advantage[®]Plus 55 for Dogs (EPA Reg. No. 11556-127) Advantage[®]Plus 100 for Dogs (EPA Reg. No. 11556-130)

Dear Ms. Eagle:

Enclosed with this cover letter are applications for amendment of the registration of four (4) companion animal spot-on products, named Advantage® Plus 10 for Dogs (EPA Reg No. 11556-128), Advantage® Plus 20 for Dogs (11556-125), Advantage® Plus 55 for Dogs (11556-127) and Advantage® Plus 100 for Dogs (11556-130), as well as all the appropriate supporting documents and data. The purpose of this cover letter is to provide an explanatory overview of the submission which may aid in the processing of the enclosed information and respective registration applications.

Purpose of Registration Action: Bayer HealthCare, Animal Health Division, is proposing to revise the claims on the labels of the four

Bayer HealthCare LLC Animal Health P.O. Box 390 Shawnee Mission, KS 66201-0390 Ms. Venus Eagle Document Processing Desk (REGFEE) Office of Pesticide Programs (7504P) U.S. Environmental Protection Agency

Page 2 December 7, 2009

Advantage Plus for Dogs products to change the opening instructions and make minor label updates and modifications both desired by Bayer and recommended or permitted by the Agency. To change the opening instructions, additional Child Resistant Packaging studies were conducted and are enclosed for Agency review.

Child Resistant Packaging Testing: As the Agency's files will show, because the acute oral toxicity value for the product formulation is below the 1500 mg/kg "trigger," and because this is a residential use, the products must be marketed in Child-Resistant Packaging (CRP). We currently have acceptable CRP packaging data on file with the Agency (and the respective CRP Certification letters), but it is our desire to replace the current packaging with a different CRP packaging material. We chose to revise the opening instructions at the same time. These new opening instructions were used in the enclosed CRP testing studies. The testing design to satisfy the requirements for all product presentations was developed with the agreement of the Agency's expert, Dr. Rosalind Gross.

With regard to the overall CRP testing of the various packaging configurations, Bayer is aware of PR Notice 97-9 regarding the electronic submission of CRP test data, and therefore these data have been prepared appropriately and are included on CDs. CRP certification letters are also enclosed.

Packaging: The revised packaging for the products will be identical to the packaging used with the currently registered Advantage[®] products for dogs (EPA Reg. Nos. 11556-117, -119, 120, and −122) except that the tubes will be in a Child-Resistant blister. The packaging for the products will consist of a cardboard box with all appropriate label text except for the full directions for use. Inside the box will be a leaflet containing all the label text. Also inside the box will be a CRP blister package containing either 4 or 6 tubes of the appropriate size. CRP testing was done on both the 4-and 6-pack configurations of each product.

Label Modifications: The enclosed draft labeling, date of draft 12/07/09, has been revised from previous draft labeling versions (date of draft 9/17/2007) to remove redundancy, to change the opening instructions, and make minor label updates and modifications both desired by Bayer and recommended or permitted by the Agency. See Amendment attachments for detailed information. Enclosed is an identical copy of the aforementioned draft label, with the respective revisions highlighted for

Ms. Venus Eagle Document Processing Desk (REGFEE) Office of Pesticide Programs (7504P) U.S. Environmental Protection Agency

Page 3 December 7, 2009

the Agency's convenience. Although we are proposing minor modifications to the labels, these changes are minor and do not warrant nor require any additional data. Therefore, no additional data are enclosed beyond those required for CRP certification.

I hope this overview cover letter is helpful in processing the attached applications. If you have any questions, please do not hesitate to call me at (913) 268-2751.

Sincerely,

Mary Hunf 507 Douglas A. Spilker. Ph. D.

Manager, EPA Regulatory Affairs

Doug.Spilker.b@Bayer.com

DAS/lt

Enclosures

Document Processing Desk (REGFEE)
Office of Pesticide Programs (7504P)
U.S. Environmental Protection Agency
Room S-4900, One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202-4501

Enclosures:

Advantage Plus 10 for Dogs

- 1 copy proof of PRIA payment
- 1 copy Advantage Plus 10 for Dogs Application for Pesticide Registration with Application Attachment and two Appendices:

Appendix 1 – Advantage Plus 10 for Dogs Registration Notice Appendix 2 – CRP Correspondence

- 5 copies draft labels, date of draft 12/07/09
- 1 copy draft label, date of draft 12/07/09 (highlighted)
- 1 copy CRP Certification letter
- 1 copy data matrix (confidential)
- 1 copy public data matrix
- 3 copies data transmittal document
- 3 copies Bayer Report No. 33729 (Child Resistant Packaging Study; 4-pack/child)
- 3 copies Bayer Report No. 33730 (Child Resistant Packaging Study; 4-pack/adult)
- 3 copies Bayer Report No. 33731 (Child Resistant Packaging Study; 6-pack/child)
- 3 copies Bayer Report No. 33732 (Child Resistant Packaging Study; 6-pack/adult)
- 1 copy CD transmittal document
- 1 CD (electronic data file) for Bayer Report No. 33729
- 1 CD (electronic data file) for Bayer Report No. 33730
- 1 CD (electronic data file) for Bayer Report No. 33731
- 1 CD (electronic data file) for Bayer Report No. 33732

Advantage Plus 20 for Dogs

- 1 copy proof of PRIA payment
- 1 copy Advantage Plus 20 for Dogs Application for Pesticide Registration with Application Attachment and two Appendices:

Appendix 1 - Advantage Plus 20 for Dogs Registration Notice

Appendix 2 – CRP Correspondence

- 5 copies draft labels, date of draft 12/07/09
- 1 copy draft label, date of draft 12/07/09 (highlighted)

- 1 copy CRP Certification letter
- I copy data matrix (confidential)
- 1 copy public data matrix
- 3 copies data transmittal document
- 3 copies Bayer Report No. 33725 (Child Resistant Packaging Study; 4-pack/child)
- 3 copies Bayer Report No. 33726 (Child Resistant Packaging Study; 4-pack/adult)
- 3 copies Bayer Report No. 33727 (Child Resistant Packaging Study; 6-pack/child)
- 3 copies Bayer Report No. 33728 (Child Resistant Packaging Study; 6-pack/adult)
- 1 copy CD transmittal document
- 1 CD (electronic data file) for Bayer Report No. 33725
- 1 CD (electronic data file) for Bayer Report No. 33726
- I CD (electronic data file) for Bayer Report No. 33727
- 1 CD (electronic data file) for Bayer Report No. 33728

Advantage Plus 55 for Dogs

- 1 copy proof of PRIA payment
- I copy Advantage Plus 55 for Dogs Application for Pesticide Registration with Application Attachment and two Appendices:

Appendix 1 – Advantage Plus 55 for Dogs Registration Notice

Appendix 2 - CRP Correspondence

- 5 copies draft labels, date of draft 12/07/09
- 1 copy draft label, date of draft 12/07/09 (highlighted)
- 1 copy CRP Certification letter
- 1 copy data matrix (confidential)
- 1 copy public data matrix
- 3 copies data transmittal document
- 3 copies Bayer Report No. 33721 (Child Resistant Packaging Study; 4-pack/child)
- 3 copies Bayer Report No. 33722 (Child Resistant Packaging Study; 4-pack/adult)
- 3 copies Bayer Report No. 33723(Child Resistant Packaging Study; 6-pack/child)
- 3 copies Bayer Report No. 33724(Child Resistant Packaging Study; 6-pack/adult)
- 1 copy CD transmittal document
- I CD (electronic data file) for Bayer Report No. 33721
- 1 CD (electronic data file) for Bayer Report No. 33722
- 1 CD (electronic data file) for Bayer Report No. 33723
- 1 CD (electronic data file) for Bayer Report No. 33724

Transmittal Document

1. Name and Address of Submitter

Bayer HealthCare LLC Animal Health Division

Box 390

Shawnee Mission, Kansas 66201-0390

Douglas A. Spilker, Ph.D.

Manager, EPA Regulatory Affairs

(913) 268-2751

2. Regulatory Action in Which this Package is Submitted

Data submitted to support revised label claim for Advantage® Plus 10 for Dogs (EPA Reg. No. 11556-128)

3. <u>Transmittal Date</u> December 7, 2009

4. List of Submitted Studies:

MRID No.	<u>Volume</u>	
47932301	1 -	"Child-Resistant Packaging (CRP) Child Panel Test of 4 x 0.40 mL Advantage® IGR KISI Blisters for Dogs," 40 CFR Part 157.20 and 16 CFR Part 1700.20, L. M. Dixon, Report No. 33729, 58 p.
47932302	2 -	"Child-Resistant Packaging (CRP) Senior Adult Panel Test of 4 x 0.40 mL Advantage® IGR KISI Blisters for Dogs," 40 CFR Part 157.20 and 16 CFR Part 1700.20, L. M. Dixon, Report No. 33730, 251 p.
47932303	3 -	"Child-Resistant Packaging (CRP) Child Panel Test of 6 x 0.40 mL Advantage® IGR KISI Blisters for Dogs," 40 CFR Part 157.20 and 16 CFR Part 1700.20, L. M. Dixon, Report No. 33731, 56 p.
47932304	4 -	"Child-Resistant Packaging (CRP) Senior Adult Panel Test of 6 x 0.40 mL Advantage® IGR KISI Blisters for Dogs," 40 CFR Part 157.20 and 16 CFR Part

1700.20, L. M. Dixon, Report No. 33732, 250 p.

Bayer HealthCare Animal Health



Bayer HealthCare LLC Animal Health P.O. Box 390

Shawnee Mission, KS 66201-0390

Via Federal Express

December 7, 2009

Document Processing Desk (NO REGFEE – Additional Information)
Office of Pesticide Programs (7504P)
U.S. Environmental Protection Agency
Room S-4900, One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202-4501

Attention: Ms. Venus Eagle (PM01)

Registration Division

Subject: Advantage® Plus 10 for Dogs

(EPA Reg. No. 11556-128)

Child-Resistant Packaging Certification

Dear Ms. Eagle:

I certify that the packaging that will be used for this product meets the standard of 40 CFR 157.32.

Sincerely,

Douglas A. Spilker. Ph. D.

Manager, EPA Regulatory Affairs

Doug.Spilker.b@Bayer.com

DAS/lt



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY 1200 Pennsylvania Avenue, N.W. WASHINGTON, D.C. 20460

Paperwork Reduction Act Notice: The public reporting burden for this collection of informatic and 0.25 hours per response for reregistration and special review activities, including time for necomments regarding burden estimate or any other aspect of this collection of information, inclustrategies Divisioo (2822T), U.S. Environmental Protection Agency, 1200 Pennsylvania Avendo this address.	eading the instructions iding suggestions far r	and completing the necessary forms. Send educing the burden to: Director, Collection							
Certification with Respect to Citation of Data									
Applicant's/Registrant's Name, Address, and Telephone Number Bayer HealthCare LLC, Animai Health DlvIsion, PO Box 390, Shawпee Mission, KS	Applicant's/Registrant's Name, Address, and Telephone Number Bayer HealthCare LLC, Animai Health Division, PO Box 390, Shawnee Mission, KS 66201 EPA Registration Number/File Symbol 11556-128								
Active Ingredient(s) and/or representative test compound(s) midacloprid, pyriproxyfen Decamber 18, 2009									
General Use Pattern(s) (list all those claimed for this product using 40 CFR Part 158) Indoor, residential Product Name Advantage Plus 10 for Dogs									
NOTE: If your product is a 100% repackaging of another purchased EPA-registered product labeled for all the same uses on your label, you do not need to submit this form. You must submit the Formulator's Exemption Statement (EPA Form 8570-27).									
I am responding to a Oata-Call-In Notice, and have included with this form a list of companies sent offers of compensation (the Data Matrix form should be used for this purpose).									
SECTION I: METHOD OF DATA SUPP	ORT (Check one me	ethod only)							
I am using the cite-all method of support, and have included with this form a list of companies sent offers of compensation (the Data Matrix form should be used for this purpose). I am using the selective method of support (or cite-all option under the selective method), and have included with this for completed list of data requirements (the Data Matrix form in used).									
SECTION II: GENERAL OFFER TO PAY									
	(Required if using the cite-all method or when using the cite-all option under the selective method to satisfy one or more data requirements) I hereby offer and agree to pay compensation, to other persons, with regard to the approval of this application, to the extent required by FIFRA.								
SECTION III: CERTI	FICATION								
I certify that this application for registration, this form for reregistration, or thi application for registration, the form for reregistration, or the Data-Call-In response. In indicated in Section I, this application is supported by all data in the Agency's files that substantially similar product, or one or more of the ingredients in this product; and (2) is	I certify that this application for registration, this form for reregistration, or this Data-Call-In response Is supported by all data submitted or cited in the application for registration, the form for reregistration, or the Data-Call-In response. In addition, if the cite-all option or cite-all option under the selective method is indicated in Section I, this application is supported by all data in the Agency's files that (1(concern the properties or effects of this product or an identical or substantially similar product, or one or more of the ingredients in this product; and (2) is a type of data that would be required to be submitted under the data requirements in effect on the date of approval of this application if the application sought the initial registration of a product of identical or similar composition and uses.								
I certify that for each exclusive use study cited in support of this registration the written permission of the original data submitter to cite that study.	or reregistration, tha	It I am the original data submitter or that I have obtained							
I certify that for each study cited In support of this registration or reregistration that is not an exclusive use study, either: (a) I am the original data submitter to use the study in support of this application; (c) all periods of eligibility for compensation have expired for the study; (d) the study is in the public literature; or (e) I have notified in writing the company that submitted the study and have offered (i) to pay compensation to the extent required by sections 3(c)(1)(F) and/or 3(c)(2)(B) of FIFRA; and (ii) to commence negotiations to determine the amount and terms of compensation, if any, to be paid for the use of the study.									
I certify that in all instances where an offer of compensation is required, cop- accordance with sections 3(c)(1)(F) and/or 3(c)(2)(B) of FIFRA are available and will be evidence to the Agency upon request, I understand that the Agency may initiate action FIFRA.	e submitted to the A	gency upon request. Should I fail to produce such							
i certify that the statements i have made on this form and all attach me knowingly false or misleading statement may be punishable by fine or imprisor									
Signature Mary Heat	Date 12/18/2009	Typed or Printed Name and Tille Mary M. Hunt, Regulatory Pesticides Mgr							

EPA Form 8570-34 (12-2003) Electronic and Paper versions available. Submit only Paper version.



Approved OMB No. 2070-0060

	send the form to the address,	·····	DATA	MATRIX		· · · · · · · · · · · · · · · · · · ·
Dater Decembe	Date: December 7, 2009			o./File Syml	11556-128, 11556-127 11556-125, 11556-130	Page 1 of 12
Bayer HealthCare LLC Animal Health Division P.O. Box 390 Shawnee Mission, KS 66201-0390			A	dvantage® ! dvantage® i	Plus 10 for Dogs Plus 20 for Dogs Plus 55 for Dogs Plus 100 for Dogs	Ingredient: Imidacloprid, CAS = 138261-41-3 Pyriproxyfen, CAS = 95737-68-1
Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Report Number	Description
 Product Chemi	stry, Section 158.240					
	******	42055302	264	PER	BR 1759 (TGAI)	
		43306001	264	PER	BR 1879 (TGAI)	
61-I	Chemical identity	42256302	264	PER	BR 1766 (Formulation)	
		42055302	264	PER	BR 1759 (TGA1)	
		43306001	264	PER	BR 1879 (TGAI)	
	1	42270801	264	PER	BR 1785 (TGAI)	
61-2	Statement of Composition	42256302	264	PER	BR 1766 (Formulation)	
		42055302	264	PER	BR 1759 (TGAI)	
61-3	Formation of impurities	42256302	264	PER	BR 1766 (Formulation)	
	The state of the s	42055303	264	PER	BR 1760 (TGAI)	
		43306002	264	PER	BR 1880 (TGAI)	
		42270802	264	PER	BR 1786 (TGAI)	
62-1	Preliminary analysis	42256302	264	PER	BR 1766 (Formulation)	
		42055303	264	PER	BR 1760 (TGAI)	
		43306002	264	PER		5 5 78 70 5 5 5
62-2	Certification of limits	42256302	264	PER	BR 1766 (Formulation)	62 1 3 60 2 6 1 9 60 2
	·	42055303	264	PER	BR 1760 (TGAI)	0 0 0 0 0 0 0
	<u> </u>	43213001	264	PER	BR 1874 (1'GAI)	
		43306002	264	PER	BR 1880 (TGAI)	64 677 676 67°
	Table Park	42256302	264	PER	BR 1766 (Formulation) 2 2	, , , , ,
62-3	Analytical method	45096901	11556	OWN	Report No. 75130 2 2 2 2 2	8, 94 7 9 22



Approved OMB No. 2070-0060

20400. Do itol S	end the form to the address.		DATA	MATRIX		
Date: December	Date: December 7, 2009				ol: 11556-128, 11556-127 11556-125, 11556-130	Page 2 of 12
Bayer HealthCare LLC Animal Health Division P.O. Box 390 Shawnee Mission, KS 66201-0390			A	dvantage® F	Plus 10 for Dogs Plus 20 for Dogs	Ingredient: Insidacloprid, CAS = 138261-41-3
					Plus 55 for Dogs Plus 100 for Dogs	Pyriproxyfen, CAS = 95737-68-1
Gnideline Reference Number	Guideline Study Name	MRID Number	Submitter	Slatus	Note Report Number	Description
	<u> </u>	42055304	264	PER	BR 1761 (TGAI)	
63-1	Chemical and Physical Properties	42256302	264	PER	BR 1766 (Formulation)	
	· ·	42055304	264	PER	BR 1761 (FGAI)	
63-2	Арреагансе	42256302	264	PER	BR 1766 (Formulation)	
		42055304	264	PER	BR 1761 (TGAI)	
63-3	Physical state	42256302	264	PER	BR 1766 (Formulation)	
		42055304	264	PER	BR 1761 (TGAI)	
63-4	Odor	42256302	264	PER	BR 1766 (Formulation)	
63-5	Melting point	42055304	264	PER	BR 1761 (TGAI)	
63-6	Boiling point	42055304	264	PER	BR 1761(TGAI)	
		42055304	264	PER	BR 1761 (TGAI)	
63-7	Density	43356302	264	PER	BR 1761 (Formulation)	
63-8	Solubility	42055304	264	PER	BR 1761 (TGAI)	
63-9	Vapor pressure	42055304	264	PER	BR 1761 (TGAI)	
63-10	Dissociation constant					N.A Does not dissociate
63-11	Octanol / water partition	42055304	264	PER	BR 1761 (TGAI) 2 2 2	3 3 3
	1	42055304	264	PER	BR 1761 (TGAI)	<u> </u>
63-12	pH Hq	42256302	264	PER	BR 1766 (Formulation) " අය	
63-13	Slability	42055304	264	PER	BR 1761 (TGAI)	
63-14	Oxidizing / reducing action		264	PER	22.2	NA - No exidating par reductive characteristics
63-15	Flammability	42055304	264	PER		
63-16	Explodability	42055304	264	PER	BR 1761 (TGAI)	



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			DATA	MATRIX		
Date: December 7, 2009 Bayer HealthCare LLC Animal Health Division P.O. Box 390 Shawnee Mission, KS 66201-0390			EPA Reg No	o./File Symb	nol: 11556-128, 11556-127 11556-125, 11556-130	Page 3 of 12 Ingredient: Imidaeloprid, CAS = 138261-41-3 Pyriproxyfen, CAS = 95737-68-1
			A A	.dvanlage® l .dvanlage® l	Plus 10 for Dogs Plus 20 for Dogs Plus 55 for Dogs Plus 100 for Dogs	
Guideline Reference Yumber	Guideline Study Name	MRID Number	Submitter	Status	Note Report Number	Description
		42055304	264	PER	BR 1761 (TGAI)	
63-17	Storage stability	42256302	264	PER	BR 1766 (Formulation)	
63-18	Viscosity		264	PER		N.A Solîd
63-19	Miseibility		264	PER		N.A Solid
63-20	Corrosion eluaracteristics	42055304 42256302	264 264	PER PER	BR 1761 (TGAI) BR 1766 (Formulation)	
63-21	Dielectrie breakdown volt		<u> </u>			N.A Solid
64-1	Submittal of samples				Samples available upon request	
830-Group A	Product Chemistry: Identity, Composition, Analysis	45096902	11556	OWN	Report No. 75133	
830-Group B	Product Chemistry: Physical/Chemical Properties	45096903	11556	OWN	Report No. 75132	
Wildlife and Aqu	atic Organisms, Section 158.490					
71-1	Acute avian oral - quail/duck	<u> </u>				N.A.
71-2(a)	Avian dietary - quail					N.A.
71-2(b)	Avian dietary - duck				0 2	N;A. 2222
71-3	Wild mammal toxicity				9997	oliga. ""?
71-4(a)	Avian reproduction - quail			1	6 2 3	aN.A. 0000
71-4(b)	Avian reproduction – duck					N.A.
71-5	Simulated or actual field study					NA no no
72-1(a)	Fish toxicity - bluegill				5 0 0 0	N.A. 2
72-t(b)	Fish toxicity blucgill - tep				* * * * * * * * * * * * * * * * * * * *	, N.A., " a o o o
72-2(a)	Invertebrate toxicity - Daphnia				2 6 0	N.Ä.



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·····				MATRIX		·
Date: December 7, 2009			EPA Reg No	o./File Symb	ol: 11556-128, 11556-127 11556-125, 11556-130	Page 4 of 12
Bayer HealthCare LLC Animal Health Division P.O. Box 390			A	.dvantage® F	Plus 10 for Dogs Plus 20 for Dogs	Ingredient: Imidaeloprid, CAS = 138261-41-3
7.0. dux 390 Shawnee Mission,	KS 66201-0390				Plus 55 for Dogs	Pyriproxyfen, CAS = 95737-68-1
71 m 1/1300 1/1331071,	1	1	A	ovantagew i	Plus 100 for Dogs	<u> </u>
Guideline Roforence Numbor	Guideline Study Name	MRID Number	Submitter	Status	Note Report Number	Description
72-2(b)	Invertebrate toxicity - Amplupods	<u> </u>	Τ	1		N.A.
72-2(c)	Acute aquatic invertebrate toxicity - Chironomids					N.A.
72-3(a)	Estuarine / marine toxicity - fish					N.A.
72-3(b)	Estuarine / marine toxicity - mollusk					N.A.
72-3(c)	Estuarine/marine toxicity - shrimp					N.A.
72-4(a)	Early life stage - fish					N.A.
72-4(b)	Life cycle invertebrate					N.A.
72-7	Simulated or actual field study					N.A.
None	Foliar half-life and distribution for potatoes					N.A.
None	Runoff and Erosion predictions for apple/potato/cotton		A STATE OF THE STA			N.A.
None	Risk assessment for apple/potato/cotton					N.A.
None	PELMO Modeling - sugarbeet/Germany					N.A.
Foxicology, Section	on 158.340					
		42055331	264	PER	Report No. 100040 (TGAI)	
		42256313	264	PER	Report No. 100010 (2 F)	5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5
		43428201	264	PER	Report No. 106380 (1.6 F)	0 0 0 0
		43679601	11556	OWN	Report No. 74585 (Adv)	20000
970 1 100	A cuta coal tauricity and	45096904	11556	OWN	Report No. 75195 (Adv Plus)	
870.1100	Acute oral toxicity rat	47089411	11556	OWN	Report No. 75922 (Adv Plus)	<u> </u>



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			DATA	MATRIX		
Pate: December 7, 2009			EPA Rcg No	./File Symb	ol: 11556-128, t1556-127 11556-125, 11556-130	Page 5 of 12
tyer HealthCare LLC timal Health Division O. Box 390 awnee Mission, KS 66201-0390		-	A A	dvantage® I dvantage® I	Plus 10 for Dogs Plus 20 for Dogs Plus 55 for Dogs Plus 100 for Dogs	Iogredicnt: lmidacloprid, CAS = 138261-41-3 Pyriproxyfen, CAS = 95737-68-1
·			···	1.	Note	
ideline ference mber	Guideline Study Name	MR1D Number	Submitter	Status	Report Number	Description
		pro	,			
		42055332	264	PER	Report No. 100041 (TGAI)	
		42256315	264	PER	Report No. 100002 (2 F)	
		43428201	264	PER	Report No. 106380 (1.6 F)	
		4379602	11556	OWN	Report No. 74584 (Adv)	
870.1200	Acute dermal toxicity, rat/rabbit	45096905	11556	OWN	Report No. 75196	
		42055333	264	PER	Report No. 99806 (TGAt)	
	.					
		42286101	264	PER	Report No. 99806-1 (TGAt)	
		42286101 42256317	264 264	PER	Report No. 99806-1 (TGAt) Report No. 100012 (2 F)	
		42256317 43428201	264 264	PER PER	Report No. 100012 (2 F) Report No. 106380 (1.6 F)	
		42256317	264	PER	Report No. 100012 (2 F)	
870.1300	Aente inhalation toxicity, rat	42256317 43428201	264 264	PER PER OWN	Report No. 100012 (2 F) Report No. 106380 (1.6 F)	
870.1300	Acute inhalation toxicity, rat	42256317 43428201 43679603	264 264 11556	PER PER OWN	Report No. 100012 (2 F) Report No. 106380 (1.6 F) Report No. 74589 (Adv)	
870.1300	Aente inhalation toxícity, rat	42256317 43428201 43679603 45096906	264 264 11556	PER PER OWN	Report No. 100012 (2 F) Report No. 106380 (1.6 F) Report No. 74589 (Adv) Report No. 75197 (Adv Plus)	
870.1300	Aente inhalation toxícity, rat	42256317 43428201 43679603 45096906 42055334	264 264 11556 11556 264	PER PER OWN OWN PER	Report No. 100012 (2 F) Report No. 106380 (1.6 F) Report No. 74589 (Adv) Report No. 75197 (Adv Plus) Report No. 99679 (TGAI)	
870.1300	Aente inhalation toxicity, rat	42256317 43428201 43679603 45096906 42055334 42256319	264 264 11556 11556 264 264	PER PER OWN OWN PER PER	Report No. 100012 (2 F) Report No. 106380 (1.6 F) Report No. 74589 (Adv) Report No. 75197 (Adv Plus) Report No. 99679 (TGAI) Report No. 99815 (2 F)	

45096907

t t556

OWN

Report No. 75199 (Adv Plus)

Primary eye irritation - rabbit

870,2400



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Date: December 7, 2009			er 7, 2009 EPA Reg No./File Symbol: 11556-128, 11556-127 11556-125, 11556-130					
Animal Health D P.O. Box 390	Bayer HealthCare LLC Animal Health Division P.O. Box 390 Shawnee Mission, KS 66201-0390				lus 10 for Dogs lus 20 for Dogs lus 55 for Dogs lus 100 for Dogs	Ingredient: Imidaeloprid, CAS = 138261-41-3 Pyriproxyfen, CAS = 95737-68-1		
Guideline Reference Number	eference Number		Submitter	Status	Note Report Number	Description		

870,2600	Dermal sensitization - guinca pig	45096909	11556	OWN	Report No. 75201 (Adv Plus)	
_		43170301	264	PER	Report No. 106348	
81-8(SS)	Acute neurotoxicity	43285801	264	PER	Report No. 106348-1	
82-1(a)	90-day feeding - rodent	42256327	264	PER	Report No. 100036	
82-1(b)	90-day feeding - non-rodent	42256328	264	PER	Report No. 100176	
		··•		-	<u> </u>	
82-2	21-day dermal - rabbit/rat	42256329	264	PER	Report No. 100688	
82-5(b)	90 day neurotoxicity - manunal	43286401	264	PER	Report No. 106356	<u> </u>
		42256331	264	PER	Report No. 100652	
		42256332	264	PER	Report No. 101931	
				.		
		42256333	264	PER	Report No. 102658	
83-1(a)	Chronic feeding toxicity - rodent	42256334	264	PER	Report No. 99672	
83-1(a)						
	Chronic feeding loxicity - non-rodent	42273002	264	PER	Report No. 100015	



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Date: December 7, 2009 Bayer HealthCare LLC Animal Health Division P.O. Box 390 Shawnee Mission, KS 66201-0390			EPA Reg N	o./File Symt	ool: 11556-128, 11556-127 11556-125, 11556-130	Page 7 of 12 Ingredient: Imidaeloprid, CAS = 138261-41-3 Pyriproxyfen, CAS = 95737-68-1
			A .	\dvantage® \dvantage®	Plus 10 for Dogs Plus 20 for Dogs Plus 55 for Dogs Plus 100 for Dogs	
				Id valuage 87	Note	
Guideline Reference Number	Guidefine Study Name	MRID Number	Submitter	Status	Report Number	Description
		42256331	264	PER	Report No. 100652	
		42256332	264	PER	Report No. 101931	
		42256333	264	PER	Report No. 102658	
83-2(a)	Oneogenicity - rat	42256334	264	PER	Report No. 99672	
		42256335	264	PER	Report No. 100693	
		42256336	264	PER	Report No. 101929	
83-2(b)	Oneogenicity - mouse	42256337	264	PER	Report No. 99808	
83-3(a)	Developmental toxicity - rat	42256338	264	PER	Report No. 98571	
83-3(b)	Developmental toxicity - rabbit	42256339	264	PER	Report No. 98572	
83-4	Two generation reproduction - rat	42256340	264	PER	Report No. 100647	
		42256341	264	PER	Report No. 101276	
		42256342	264	PER	Report No. 98584	
84-2(a)	Gene mutation (ames test)	42256343	264	PER	Report No. 98570	
		42256344	264	PER	Report No. 100021	
		42256345	264	PER	Report No. 99262	
		42256346	264	PER	Report No. 99257	
		42256347	264	PER	Report No. 102652	
	Structural chromosomal aberration	42256348	264	PER	Report No. 102654	
84-2(b)		42256349	264	PER	Report No. 102655	
		42256350	264	PER	Report No. 99676	
		42256351	264	PER	Report No. 101275	
04.4	Other america offert	42256352	264	PER	Report No. 98573	
84-4	Other genotoxic effects	42256353	264	PER	Report No. 102653	



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Bayer HealthCare LLC Animal Health Division P.O. Box 390		A	dvantage® F	Plus 10 for Dogs Plus 20 for Dogs Plus 55 for Dogs	Ingredient: Imidacloprid, CAS = 138261-41-3 Pyriproxyfen, CAS = 95737-68-1	
Shawnec Missio	n, KS 66201-0390				Plus 100 for Dogs	, , , , , , , , , , , , , , , , , , ,
Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note Report Number	Description
		42256254	1 201	I pen	I B	
		42256354	264	PER	Report No. 101999	
		42256355	264	PER	Report No. 87264	
A		42256356	264	PER	Report No. 87265	
1-85 	General metabolism	42256357	264	PER	Report No. 102617	
		43679607	11556	OWN	Report No. 74580 (Adv) Report No. 74590 (Adv)	Dogs
		43679608 44099801	11556	OWN	Report No. 74730 (Adv)	Dogs
870,7200		45097102	11556	OWN	Report No. 75121 (Adv Plus)	Puppies Dogs
(86-1)	Doniestic Animal Safety	45097102	11556	OWN	Report No. 75119 (Adv Plus)	Puppies
(30-1)	Donestic Athmat Safety	43679503	11556	OWN	Report No. 74571 (Adv)	Cats
		43679504	11556	OWN	Report No. 74581 (Adv)	Cats
		43679609	11556	OWN	Report No. 74572 (Adv)	Dogs
		43679610	11556	OWN	Report No. 74541 (Adv)	Dogs
		44256901	11556	OWN	Report No. 74800 (Adv)	Speed of flea kill
		44256902	11556	OWN	Report No. 47828 (Adv)	Larvieidal efficacy
		44256903	11556	OWN	Report No. 74792 (Adv)	Effects of shampooing
		47109101	11556	OWN	Report No. 75867 (K9)	Waterproof
		45086801	1021	PER	Report No. OT018-94	Pyriproxyfen efficacy
		45086801	1021	PER	Report No. OT016-93	Pyriproxyfen efficaey
		45086801	1021	PER	Report No. OT006-96	Pyriproxyfen efficaey
95-9	Efficacy	47190401	11556	OWN	Report No. 75950 (Advantage)	Lice
Plant Protection IS8.S40	, Section		•	•		
122-2	Aquatic plant growth					N.A.
123-2	Aquatic plant growth	··	1			N.A.



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Bayer HealthCare LLC Animal Health Division P.O. Box 390 Shawnee Mission, KS 66201-0390		EPA Reg No./File Symbol: 11556-128, 11556-127 11556-125, 11556-130				Page 9 of 12	
		A A	Advantage® P Advantage® P	lus 10 for Dogs lus 20 for Dogs lus 55 for Dogs lus 100 for Dogs	Ingredient: Imidaeloprid, CAS = 138261-41-3 Pyriproxyfen, CAS = 95737-68-t		
Guidetine Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note Report Number	Description	

Non-Target Ins Section 158.590	ects,	
141-1	Honey bee acute contact	N.A.
141-2	14oncy bee residue on foliage	N.A.
Reentry Protee Section 158.390		
230-236	Mixer/loader/applicator exposure	N. A.
Environmental Section 158.290		
161-1	Hydrolysis	N.A.
161-2	Photodegradation - water	N.A.
161-3	Photodegradation - soil	N.A.
162-1	Aerobie soil metabolism	N.A.
162-2	Anerobie soil metabolism	N.A.
162-3	Anaerobie aquatie metabolism	N.A.
163-1	Leaching / adsorption/desorption	N.A.
164-1	Terrestrial field dissipation	N.A.
165-1	Confined rotational crop	N.A.
165-2	Field rotational crop	N.A.
166-1	Ground water - small prospective	N.A.
None	Environmentat fate summary	N.A.



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			DATA	MATRIX		-
Date: December 7, 2009		EPA Reg No	o./Filc Symbo	: 11556-128, 11556-127 11556-125, 11556-130	Page 10 of 12	
Bayer HealthCare LLC Animal Health Division P.O. Box 390 Shawnee Mission, KS 66201-0390		A	Advantage® Pl Advantage® Pl	is 10 for Dogs is 20 for Dogs is 55 for Dogs is 100 for Dogs	Ingredient: Imidacloprid, CAS = 138261-41-3 Pyriproxyfen, CAS = 95737-68-1	
Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note Report Number	Description

Residue, Section	n 158.240					
171-4(a)	Nature of residue - plants			1		N,A.
171-4(b)	Nature of residue - livestock and poultry			1		N.A.
171-4(c)	Residue analytical method - plants					N.A.
171-4(d)	Residue analytical method - animal					N.A.
171-4(e)	Storage stability					N.A.
171-4(j)	Magnitude of residues - meat/milk/poultry/egg					N.A.
171-4(k)	Magnitude of residue - erop field trials					N.A.
171-4(1)	Magnitude of residue - processed food/feed					N.A.
171-4(m)	Method validation/nultiresidue method					N.A.
None	Benefits Reports					
None	Dictary Analysis					N.A.
Child-Reesistan	t Packaging, Section 157					
157.20	Standards - Child-Resistant Packaging Testing	47089407	11556	OWN	Report No. 75913	Aclar CRP packaging
		47089408	11556	OWN	Report No. 75914	Aclar CRP packaging
		47089409	11556	OWN	Report No. 75915	Aclar CRP packaging
		47089410	11556	OWN	Report No. 75916	Aclar CRP packaging
		47089103	11556	OWN	Report No. 75897	Aclar CRP packaging
		47089104	11556	OWN	Report No. 75898	Aclar CRP packaging
	1	47089101	11556	OWN	Report No. 75893	Aclar CRP packaging
		47089102	11556	OWN	Report No. 75894	Aclar CRP packaging
		47089201	11556	OWN	Report No. 75905	Aclar CRP packaging
		47089202	11556	OWN	Report No. 75906	Aclar CRP packaging



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DO TOU.	send the form to the decrees.									
			DATA	A MATRIX						
Date: Decembe	er 7, 2009		EPA Reg N	o./File Symb	iol: 11556-128, 11556-127 11556-125, 11556-130	Page 11 of 12				
Bayer HealthCare LLC Animal Health Division P.O. Box 390 Shawnee Mission, KS 66201-0390		, A	Advantage® F Advantage® F	Plus 10 for Dogs Plus 20 for Dogs Plus 55 for Dogs Plus 100 for Dogs	Ingredient: Imidaeloprid, CAS = 138261-41-3 Pyriproxyfen, CAS = 95737-68-1					
Guideline Reference Number	eference		Submitter	Status	Note Report Number	Description				
		47089203	11556	OWN	Report No. 75907	Aclar CRP packaging				
		47089204	11556	OWN	Report No. 75908	Aclar CRP packaging				
		47089301	11556	OWN	Report No. 75909	Actar CRP packaging Actar CRP packaging				
		47089302	11556	OWN	Report No. 75910	Aclar CRP packaging				
		47089303	11556	OWN	Report No. 75911	Aelar CRP packaging				
		47089304	11556	OWN	Report No. 75912	Aclar CRP packaging				
			11556	OWN	Report No. 33717	4.0 mL/4 pk/ehild (KISI) - Advantage Plus 100				
			11556	OWN	Report No. 33718	4.0 mL/4 pk/adult (KISI) - Advamage Plus 100				
			11556	OWN	Report No. 33719	4.0 mL/6 pk/ehild (KISI) – Advamage Plus 100				
			11556	OWN	Report No. 33720	4.0 mL/6 pk/adult (KISI) - Advantage Plus 100				
			11556	OWN	Report No. 33721	2.5 mL/4 pk/ehild (KISI) - Advantage Plus 55				
			11556	OWN	Report No. 33722	2.5 mL/4 pk/adult (KISI) - Advantage Plus 55				
			11556	OWN	Report No. 33723	2.5 mtJ6 pk/child (KISI) - Advantage Plus 55				
	1		11556	OWN	Report No. 33724	2.5 mL/6 pk/adult (KISI) - Advantage Plus 55				
			1 1556	OWN	Report No. 33725	1.0 mL/4 pk/child (KISI) – Advantage Plus 20				
			11556	OWN	Report No. 33726	1.0 mL/4 pk/adult (KISI) – Advantage Phis 20				
			11556	OWN	Report No. 33727	1.0 mt/6 pk/child (KISI) Advantage Plus 20				
			11556	OWN	Report No. 33728	1.0 mL/6 pk/adult (KISI) - Advantage Plus 20				
			11556	OWN	Report No. 33729	0.4 mL/4 pk/child (KISI) - Advantage Plus 10				
			11556	OWN	Report No. 33730	0.4 mL/4 pk/adnlt (KISI) - Advantage Plus 10				



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			DATA	MATRIX		
Bayer Health Care LLC Animal Health Division P.O. Box 390 Shawnee Mission, KS 66201-0390		EPA Reg No	o./File Symbo	l: 11556-128, 11556-127 11556-125, 11556-130	Page 12 of 12 Ingredient: Imidaeloprid, CAS = 138261-41-3 Pyriproxyfen, CAS = 95737-68-1	
		A A	.dvantage® Pl .dvantage® Pl	us 10 for Dogs us 20 for Dogs us 55 for Dogs us 100 for Dogs		
Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note Report Number	Description

	11556	OWN	Report No. 33731	0.4 mL/6 pk/child (KtSt) - Advantage Plus 10
	11556	OWN	Report No. 33732	0.4 mL/6 pk/adult (KtSt) - Advantage Plus 10

Signature Work A. Julia

Douglas A. Spilker Manager, EPA Regulatory Affairs

December 7, 2009



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20100, 100110(send the form to the address.					
		<u> </u>		MATRIX		
			EPA Reg No	o./File Symb	ol: 11556-128, 11556-127 11556-125, 11556-130	Page 1 of 12
			Product: Advantage® Pius t0 for Dogs Advantage® Plus 20 for Dogs Advantage® Plus 55 for Dogs Advantage® Plus 100 for Dogs			Ingredient: Imidaeloprid, CAS = 138261-41-3 Pyriproxyfen, CAS = 95737-68-1
				Τ	Note	
Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Report Number	Description
				anostestavanta		
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			11556	OWN	* * * * * * * * * * * * * * * * * * * *	



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			DATA	MATRIX			
Date: December 7, 2009 Bayer HealthCare LLC Animal Health Division P.O. Box 390 Shawnee Mission, KS 66201-0390			EPA Reg No	./File Symb	ol: 11556-128, 11556-127 11556-125, 11556-130	Page 2 of 12 Ingredient: Imidacloprid, CAS = 138261-41-3 Pyriproxyfen, CAS = 95737-68-1	
			A A	.dvantage® .dvantage®	Plus 10 for Dogs Plus 20 for Dogs Plus 55 for Dogs Plus 100 for Dogs		
Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note Report Number	Description	
		1	264	PER			
			264	PER		<u> </u>	
	3		264	PER			
			264	PER	(A)	-	
	9 (200		264	PER	1 (1) (1) (1) (1) (1) (1) (1) (1) (1) (1		
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Bayer HealthCare LLC Animal Health Division P.O. Box 390 Shawnee Mission, KS 66201-0390			Product: Advantage® Plus 10 for Dogs Advantage® Plus 20 for Dogs Advantage® Plus 55 for Dogs Advantage® Plus 100 for Dogs			Ingredient: Imidacloprid, CAS = 138261-41-3 Pyriproxyfen, CAS = 95737-68-1
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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY 401 M Street, S.W. WASHINGTON, D.C. 20460 Form

HINGTON, D.C. 20460 Form
Approved OMB No. 2070-0060

Paperwork Reduction Act Notice: The public reponing burden for this collection of information is estimated to average 0.25 hours per response for registration activities and .025 hours per response for information, including suggestions for reducing the burden to: Director, OPPE Information Management Division (2137), U.S. Environmental Protection Agency, 401 M Street, S.W., Washington, DC 20460. Do not send the form to the address.

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Douglas A. Spilker Manager, EPA Regulatory Affairs

December 7, 2009

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY WASHINGTON, D.C. 20460

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OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

Douglas Spilker, Ph.**D**Bayer HealthCare LLC, Animal Health Division P.O. Box 390
Shawnee Mission, KS 66201-0390

Dear Dr. Spilker:

Subject:

Amendment of Basic CSFs to update numerous blocks

Advantage® Plus 10 for Dogs, EPA Reg No. 11556-128 Advantage® Plus 20 for Dogs, EPA Reg No. 11556-125 Advantage® Plus 55 for Dogs, EPA Reg No. 11556-127 Advantage® Plus 100 for Dogs, EPA Reg No. 11556-130

Your Submissions dated 9/10/09

The CSFs dated 9/9/09 as referred to above, submitted in connection with your application for registration under the Federal Insecticide, Fungicide, and Rodenticide Act, as amended, are acceptable.

All previously dated Basic CSFs for these products are superseded and are considered obsolete. If you have any questions, please contact Autumn Metzger at (703) 305-5314 or metzger.autumn@epa.gov.

Sincerely,

Venus Eagle

Product Manager 01

Insecticide-Rodenticide Branch Registration Division (7505P)

PM1

	,			
EPA	A Reg. Number: //556 -/78 EPA Receipt Date: 9//	4/0	9	
<u> </u>	Check List Hem	Yes	I N	, NA
1	Application Form (EPA Form 8570-1) -signed?	X		
2	Confidential Statement of Formula (EPA Form 8570-29) - signed?	X		<u> </u>
3	Certification with Respect to Citation of Data (EPA Form 8570-34) signed?			X
4	Formulator's Exemption Statement (EPA Form 8570-27) - signed?	 		X
5	Data Matrix (EPA Form 8570-35) [Applicable, for adding me-too uses] a) Selective Method?			
	b) Cite-All Method? Applicant owns data or list only the companies offered to pay.			
	c) Public copy of Matrix provided? See PR Notice 98-5		<u>-</u>	-
6	Is Label Included? (5 copies)			×]
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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY WASHINGTON, D.C. 20460

September 17, 2009

OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

DOUGLAS A. SPILKER, PH.D. BAYER HEALTHCARE LLC ANIMAL HEALTH DIVISION PO Box 390 SHAWNEE MISSION, KS 66201-0390

PRODUCT NAME: Advantage Plus 10 for Dogs COMPANY NAME: BAYER HEALTHCARE LLC

OPP IDENTIFICATION NUMBER: EPA FILE SYMBOL: 11556-128 EPA RECEIPT DATE: 09/16/09

SUBJECT: RECEIPT OF AMENDMENT

DEAR REGISTRANT:

The Office of Pesticide Programs has received your application for an amendment and it has passed an administrative screen for completeness.

During the initial screen we determined that the application appears to qualify for fast track review. The package will now be forwarded to the Product Manager for review to determine its acceptability for fast track status.

If you have any questions, please contact Registration Division, Risk Management Team 1, at (703) 308-8045.

Sincerely,

P. & Moone

Front End Processing Staff Information Services Branch Information Technology & Resources Management Division

Fee for Service

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This package includes the following	for Division
○ New Registration	○ AD
Amendment	○ BPPD ○ RD
□ Studies? □ Fee Waiver?	Risk Mgr. 1
□ volpay % Reduction:	
Receipt No. S-	858256
EPA File Symbol/Reg. No.	11556-128
Pin-Punch Date:	9/16/2009
This item is NOT subject t	o FFS action.
Action Code:	Parent/Child Decisions:
Requested: Granted:	MON-FEE
Amount Due: \$	
Inert Cleared for Intended Use	Uncleared Inert in Product
Reviewer:	Date: <u>11709</u>
Remarks:	

Inert ingredient information may be entitled to confidential treatment

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Please read instructions	on reverse befere comple	ting form.	·	Form A	pprova	d. OMB No.	2070-0060). Approval expires 2-28
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(. Company/Product Nul 11556-128	mber			. EPA Product Me . Eagle	nager		[—	posed Classification
4. Company/Product (Na Advantage Plus 10 for	ima) Dogs			M# eam 01				, Nostricto
Bayer HealthCare LLC P. O. Box 390 Shawnee Mission, KS	Applicant <i>Hnclude ZIP</i> Co., Animal Health Division 66201-0390 this is a new address		tc E))i), my produc	t is sin	nilar or iden	tical in cor	FIFRA Section 3[c]]3) nposition and labeling
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			Section	า - IV				
I. Contact Point (Compl	lete items directly below f	or identificatio	n of individue	il to be contacted	, if noc	essary, to pi	ocess this	application.)
Name Douglas A. Spilker, Pla	ı. D. (doug.spilker.b@ba	ıyer.com)	Title Manager, E	PA Regulatory	Affairs	66.	Telephone 913-268-	No, (Include Aree Code) $2\%51_{\rm c}^{\rm c}$
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Douglas A. Spilker	, Ph. D.		10) Sept.	20	v 9	:	222

Via Federal Express

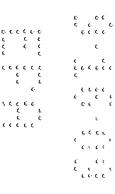
September 10, 2009

Document Processing Desk
(Amend – Non-PRIA Action)
Office of Pesticide Programs (7504P)
U.S. Environmental Protection Agency
Room S-4900, One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202-4501

Attention: Ms. Venus Eagle, PM Team 01
Registration Division

Advantage Plus 10 for Dogs (EPA Reg. 11556-128)

- a. Form 8570-1 Application for Amendment
- b. Attachment to Application (3 pages)
- c. Confidential Statement of Formula, dated 9/9/09 (2 copies)
- d. Confidential Statement of Formula, dated 3/08/07 (Supersedes)



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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY WASHINGTON, D.C. 20460

OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

Douglas A. Spilker
Bayer HealthCare LLC
Animal Health Division
P.O. Box 390
Shawnee Mission, KS 66201-0390

APR 20 2009

Dear Dr. Spilker:

Subject: Storage Stability and Corrosion Characteristics; Request for Time-Extension

EPA Registration No. 11556-125, 11556-127, 11556-128, 11556-130

Date Submitted: March 12, 2009

The Agency has received your request to extend the due date for submittal of storage stability (830.6317) and corrosion characteristics (830.6320) studies as required by Registration Notices dated September 18, 2007 for the products referenced above. These conditions of registration must be received by the Agency no later than May 31, 2010. If these conditions are not complied with, the registrations will be subject to cancellation in accordance with FIFRA section 6(e). Your release for shipment of the product constitutes acceptance of these conditions. If you have any questions regarding this letter, please contact me at (703) 306-0415.

Sincerely,

Kable Bo Davis

Entomologist

Insecticide-Rodenticide Brach Registration Division (7505P)

Bayer HealthCare Animal Health Division

Via Federal Express

March 12, 2009

Document Processing Desk (NO REGFEE)
Office of Pesticide Programs (7504P)
U.S. Environmental Protection Agency
Room S-4900, One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202-4501

Attention:

Ms. Venus Eagle/PM01

Registration Division (7505P)

Subject:

Advantage Plus 10 for Dogs (EPA Reg No. 11556-128) Advantage Plus 20 for Dogs (EPA Reg No. 11556-125) Advantage Plus 55 for Dogs (EPA Reg No. 11556-127) Advantage Plus 100 for Dogs (EPA Reg No. 11556-130)

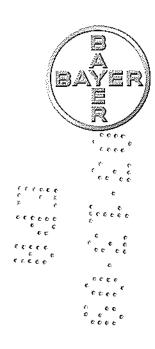
Requests for Extension in Time for Submission of

Storage Stability/Corrosion Studies:

Dear Ms. Eagle:

On September 18, 2007, the Environmental Protection Agency granted the Conditional Registration of the subject products, based on conditions among which was the submission of reports to fulfill the data requirements for storage stability (830-6317) and corrosion characteristics (830-6320). These data were to be submitted within eighteen months of the date of [the registration]. This letter is to request an appropriate extension in time for submission of these data to support the continued conditional registration of all four (4) products.

Although the registration of these products for use for flea control on dogs was granted, these products have never been produced, packaged or sold. As the Agency is aware, the original set of applications included two additional products with the identical formulation for use on cats and kittens. These registrations (11556-126 and -129) were subsequently voluntarily cancelled pursuant to Section 6(f) of FIFRA. Currently additional studies are in process to allow for Bayer Animal Health to apply for this same formulation to again be registered for use on cats and kittens.



Bayer HealthCare LLC Animal Health Division P.O. Box 390

Shawnee Mission, KS 66201

Phone: 913 268-2000

Page 2

Registration Division (7505P)

March 12, 2009

It is Bayer's intention to wait to introduce these products as a full product line into the marketplace when all of the dog and cat products have been granted EPA registration. That is, we have no intention of producing, packaging or selling any of the products with this formulation until such time as we have submitted and received the new registration of the products for use on cats and kittens. All of these products (both dog and cat) contain the identical formulation, but packaged differently depending on the sizes of the animal.

As was discussed in the meeting March 5, 2009 with you and Mr. Davis, and subsequently agreed to in the e-mail of March 10, 2009 (Kable Davis to Doug Spilker), Bayer Animal Health will start the stability and corrosion studies to support the registrations of the subject products by April 1, 2009. We further agree to provide the Agency with a 3-month interim report from the stability studies. We therefore request a revised due date of May 31, 2010, for the completion and submission of the studies to fulfill the data requirements of storage stability (830-6317) and corrosion characteristic (830-6320).

If you need further information or clarification of this request, please call me (913-268-2751).

Sincerely,

Douglas A. Spilker. Ph. D

Manager, EPA Regulatory Affairs

Doug.Spilker.b@Bayer.com

DAS/It

Material to be added to a Mini-Jacket (in the case where an e-Jacket exists)

Reg. No. 11556-128

Send to SIG: check box

This material is:

- New stamped-accepted label
- € New CSF
 - € Notification
 - € Final Printed Label
 - € Other:___

Instructions: Attach this notice on top of the material. It must be clipped all together and there should be NO-STAPLES in the material. Then give the material with this coversheet to staff in the Information Services Center (Room 230).

Reviewer's Name: 4

Phone: 306-0415 Division: RD

Date: 306-0415



U.S. ENVIRONMENTAL PROTECTION AGENCY

Office of Pesticide Programs Registration Division (7505C) t200 Pennsylvania Avc., N.W. Washington, D.C. 20460

Date of Issnance:

11556-128

EPA Reg. Number:

SEP 18 2007

NOTICE OF PESTICIDE:

X Registration

___ Reregistration (under FIFRA, as amended)

Term of Issuance:

Conditional

Name of Pesticide Product:

Advantage Plus 10 for Dogs

Name and Address of Registrant (include ZIP Code):

Bayer HealthCare LLC, Animal Health Division

P.O. Box 390

Shawnee Mission, KS 66201-0390

Note: Changes in labeling differing in substance from that accepted in connection with this registration must be submitted to and accepted by the Registration Division prior to use of the label in commerce. In any correspondence on this product always refer to the above EPA registration number,

On the basis of information lumished by the registrant, the above named pesticide is hereby registered/reregistered under the Federal Insecticide, Fungicide and Rodenticide Act.

Registration is in no way to be construed as an endorsement or recommendation of this product by the Agency. In order to protect health and the environment, the Administrator, on his motion, may at any time suspend or cancel the registration of a pesticide in accordance with the Act. The acceptance of any name in connection with the registration of a product under this Act is not to be construed as giving the registrant a right to exclusive use of the name or to its use if it has been covered by others.

This product is conditionally registered in accordance with FIFRA section 3(c)(7)(A) provided that you:

- 1. Submit and/or cite all data required for registration/reregistration of your product when the Agency requires all registrants of similar products to submit such data.
- Make the following label changes before you release the product for shipment: 2.
 - Revise the EPA Registration Number to read, "EPA Reg. No. 11556-128".
- The data requirements for storage stability (830-6317) and corrosion characteristics (830-6320) have not been satisfied, and must be submitted within eighteen months of the date of this letter.

Signature of Approving Official:

Date:

SEP 18 2007

Venus Eagle, Product Manager (01)

Insecticide-Rodenticide Branch, Registration Division (7505P)

EPA Fonn 8570-6

Page 2 EPA Reg. No. 11556-128

4. Submit one copy of the revised final printed label for the record before you release the product for shipment.

If these conditions are not complied with, the registration will be subject to cancellation in accordance with FIFRA section 6(e). Your release for shipment of the product constitutes acceptance of these conditions.

A stamped copy of the label is enclosed for your records.

Venus Eagle Product Manager (01) Insecticide-Rodenticide Branch Registration Division (7505P)

Enclosure

Supersedes: 07/10/07

NOTE TO REVIEWER: [(Brackets and parentheses indicate alternate language)]

(Front Panel)

with COMMENTS
In EPA Letter Dated:

SEP 18 2007

Advantage® Plus 10

Topical Solution

Under the Federal Insecticide, Fungicide, and Rodenticide Act, as amended, for the pesticide registered under EPA Reg. No.

Once-A-Month Topical Treatment for Fleas and Lice On Dogs and Puppies 7 Weeks and Older and 10 lbs. and Under

READ ENTIRE LABEL BEFORE EACH USE

For the Prevention and Treatment of Flea and Lice Infestations on Dogs

- Available through licensed practicing veterinarians
- For use on dogs and puppies 7 weeks of age and older
- Advantage Plus contains [imidacloprid], and [an/the] [insect growth regulator] [IGR] [pyriproxyfen] [Nylar®]*
- A single topical application remains effective for at least 4 weeks
- Convenient, easy to apply topical solution
- Once a month topical flea treatment for dogs 7 weeks of age or older
- Advantage Plus is indicated for the prevention and treatment of fleas on dogs
 7 weeks of age and older
- For the treatment and prevention of flea infestations
- One treatment prevents further flea infestations for at least 4 weeks
- Kills 98-100% of the fleas on dogs within 12 hours and continues to prevent infestations for at least four weeks
- Kills fleas before they lay eggs
- Larval flea stages in the dog's surroundings are killed following contact with an Advantage Plus treated dog
- Kills larval stages of fleas in the pet's environment
- Kills 98-100% of fleas within 12 hours of application
- Stops existing flea infestations by killing adult fleas
- Prevents reinfestations by killing adult fleas before they lay eggs
- Prevents flea eggs from latching
- Effectively breaks the flea life cycle
- Effectively targets all [life] stages of [fleas]
- 3-way flea protection ([kills] [controls] adults, larvae, and eggs)
- Prevents flea eggs [and flea larvae] from developing into [(biting) (adult)] fleas
- Treatment with Advantage Plus rapidly kills fleas and may reduce the incidence of Flea Allergic Dennatitis [FAD]

Supersedes: 07/10/07

- Flea adulticide, larvicide, and ovicide
- Prevents fleas on treated dogs from infesting (reinfesting) your home
- Kills fleas often before they bite and may reduce the risk of Canine Vector Borne Diseases (CVBD)
- Kills fleas which may serve as intermediate hosts for tapeworms
- Kills [(biting) (chewing)] lice
- For treatment and prevention of [(biting) (chewing)] lice [infestations]
- Stops existing [(biting) (chewing)] lice infestations
- Dual protection (against fleas and lice)
- Treats, prevents and controls [(biting) (chewing)] lice [infestations]
- Provides effective control of [(biting) (chewing)] lice [infestations]
- Kills [(biting) (chewing)] lice and prevents further infestations
- For treatment and prevention of infestations with [(biting) (chewing)] lice
- Remains effective after bathing and/or swimming
- Remains effective following swimming and/or shampooing
- Waterproof
- Remains effective after exposure to rain or sunlight
- Fragrance (odor) free
- In child-resistant packaging

^{*}NYLAR* - Registered trademark of McLaughlin Gormley King Co.

Active Ingredients	% By Weight
Imidacloprid; [CAS 138261-41-3]	9.10%
Pyriproxyfen; [CAS 95737-68-1]	0.46%
Other Ingredients	90.44%
Total	100.00%

KEEP OUT OF REACH OF CHILDREN CAUTION

See Below for First Aid and Precautionary Statements

PRECAUTIONARY STATEMENTS HAZARDS TO HUMANS

Harmful if swallowed. Causes moderate eye irritation. Avoid contact with eyes or clothing. Wash hands thoroughly with soap and warm water after handling.

Supersedes: 07/10/07

HAZARDS TO DOMESTIC ANIMALS

For external use only.

Do not use on puppies under 7 weeks of age.

As with any product, consult your veterinarian before using this product on debilitated, aged, pregnant or nursing animals. Individual sensitivities, while rare, may occur after using ANY pesticide product for pets. If signs persist, or become more severe, consult a veterinarian immediately. If your animal is on medication, consult your veterinarian before using this or any other product. For consumer questions call 1-800-255-6826. For medical emergencies call 1-800-422-9874.

FIRST AID

IF SWALLOWED: Call a Poison Control Center or doctor immediately for treatment advice. Have person sip a glass of water if able to swallow. Do not induce vomiting unless told to do so by the poison control center or doctor. Do not give anything to an unconscious person.

IF IN EYES: Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye. Call a poison control center or doctor for treatment advice.

IF ON SKIN: Wash with plenty of soap and water.

TO PHYSICIAN: Treat the patient symptomatically.

([Four] [Six]) 0.014 fl. oz. (0.4 mL) Tubes

EPA Est. 11556-DEU-1 EPA Reg. No. 11556-REI

Manufactured For

Bayer HealthCare LLC Animal Health Division Shawnee Mission, Kansas 66201 USA

Made in Germany

Supersedes: 07/10/07

(Back Panel)

Advantage® Plus 10

Topical Solution
Fast
Effective
Multi-Stage Flea Control

Once-A-Month Topical Treatment for Fleas and Lice on Dogs and Puppies 7 Weeks and Older and 10 lbs. and Under

- · Available through licensed practicing veterinarians
- Kills fleas within 12 hours
- Kills reinfesting fleas within 2 hours
- Prevents reinfestation for up to 4 weeks
- Convenient, easy to apply
- · Kills adults, larvae, and eggs
- · Kills chewing liee
- Waterproof
- In child-resistant packaging

READ ENTIRE LABEL BEFORE EACH USE

([Four] [Six]) 0.014 fl. oz. (0.4 mL) Tubes

Supersedes: 07/10/07

(Leaflet)

Advantage® Plus 10

Topical Solution Once-A-Month Topical Treatment for Fleas and Lice on Dogs and Puppies 7 Weeks and Older and 10 lbs. and Under

READ ENTIRE LABEL BEFORE EACH USE

For the Prevention and Treatment of Flea and Lice Infestations on Dogs.

Active Ingredients	% By Weight
Imidacloprid; [CAS 138261-41-3]	9.10%
Pyriproxyfen; [CAS 95737-68-1]	0.46%
Other Ingredients	90.44%
Total	100.00%

KEEP OUT OF REACH OF CHILDREN CAUTION

See Below for First Aid and Precautionary Statements

PRECAUTIONARY STATEMENTS HAZARDS TO HUMANS

Harmful if swallowed. Causes moderate eye irritation. Avoid contact with eyes or clothing. Wash hands thoroughly with soap and warm water after handling.

Supersedes: 07/10/07

HAZARDS TO DOMESTIC ANIMALS

For external use only.

Do not use on puppies under 7 weeks of age.

As with any product, consult your veterinarian before using this product on debilitated, aged, pregnant or nursing animals. Individual sensitivities, while rare, may occur after using ANY pesticide product for pets. If signs persist, or become more severe, consult a veterinarian immediately. If your animal is on medication, consult your veterinarian before using this or any other product. For consumer questions call 1-800-255-6826. For medical emergencies call 1-800-422-9874.

FIRST AID

IF SWALLOWED: Call a Poison Control Center or doctor immediately for treatment advice. Have person sip a glass of water if able to swallow. Do not induce vomiting unless told to do so by the poison control center or doctor. Do not give anything to an unconscious person.

IF IN EYES: Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact lenses, if present, after the first 5 minutes, then continue rinsing eye. Call a poison control center or doctor for treatment advice.

IF ON SKIN: Wash with plenty of soap and water.

TO PHYSICIAN: Treat the patient symptomatically.

DIRECTIONS FOR USE

It is a violation of Federal Law to use this product in a manner inconsistent with its labeling.

Supersedes: 07/10/07

HOW TO OPEN [4-Pack]

1. To open the blister, prepare blister card piece containing only one cavity/tube by cutting off a section of the blister card.

- 2. Do not cut close to the blister cavities.
- 3. Cut into the blister cavity across the small side close to the cap of the tube.
- 4. Peel off the cover foil and take out the tube.
- 5. Repeat steps 1 to 4 for each tube.

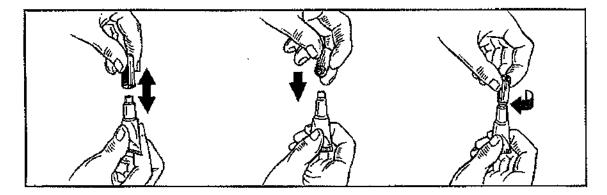
HOW TO OPEN [6-Pack]

- 1. Take a pair of scissors and cut blister card in the center of the long side into two equal portions with 3 cavities/tubes each.
- 2. Do not cut close to the blister cavities.
- 3. The two halves of the blister card can now be separated into 3 pieces with one cavity/tube each.
- 4. To open the blister, prepare blister card piece containing only one cavity/tube.
- 5. Cut into the blister cavity across the small side close to the cap of the tube.
- 6. Peel off the cover foil and take out the tube.
- 7. Repeat steps 4 to 6 for each tube.



HOW TO APPLY

- 1. Use only on dogs. Do not use on other animals.
- 2. Remove one applicator tube from the package. See "HOW TO OPEN" section.



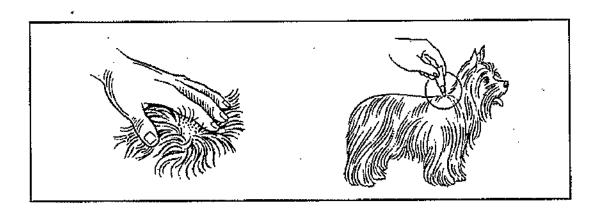
- 3. Hold applicator tube in an upright position. Pull cap off tube.
- 4. Turn the cap around and place other end of cap back on tube.

Supersedes: 07/10/07

5. Twist cap to break seal, then remove cap from tube.

6. The dog should be standing for easy application. Part the hair on the dog's back, between the shoulder blades, until the skin is visible. Place the tip of the tube on the skin and squeeze the tube twice to expel the entire contents directly on the skin.

Do not get this product in your pet's eyes or mouth.



7. Discard empty tube as described in Storage and Disposal.

The successive feeding activity of fleas on pets frequently elicits a hypersensitivity skin disorder known as flea allergy dermatitis (FAD). Treatment of pets with Advantage® Plus rapidly kills fleas and reduces the incidence of this condition.

Advantage[®] Plus kills 98-100% of the existing fleas on pets within 12 hours. Reinfesting fleas are killed within 2 hours with protection against further flea infestation lasting for up to four (4) weeks. Pre-existing pupae in the environment may continue to emerge for six (6) weeks or longer depending upon the climatic conditions.

Fleas, eggs and larvae in the pet's surroundings are killed following contact with an Advantage® Plus treated pet. Advantage® Plus provides multi-stage flea control effectively breaking all flea life-cycle stages for quick and lasting control of flea populations.

Advantage[®] Plus kills adult fleas quickly, inhibits the development of immature flea life stages and prevents them from reaching the biting adult stage.

Supersedes: 07/10/07

Advantage® Plus is waterproof and remains efficacious following a shampoo treatment, swimming or after exposure to rain or sunlight.

Monthly treatments are required for optimal control and prevention of fleas.

If re-treatment becomes necessary earlier than four weeks, do not re-treat more than once weekly.

STORAGE AND DISPOSAL

Do not contaminate water, food or feed by storage or disposal.

If Empty: Do not reuse this container. Place in trash or offer for recycling if available. If partly filled: Call your local solid waste agency or (1-800-422-9874) for disposal instructions. Never place umised product down any indoor or outdoor drain.

LIMITED WARRANTY AND LIMITATION OF DAMAGES

Bayer HealthCare LLC, Animal Health Division warrants that this material conforms to the chemical description on the label. TO THE EXTENT CONSISTENT WITH APPLICABLE LAW, BAYER MAKES NO OTHER EXPRESS OR IMPLIED WARRANTY, INCLUDING ANY OTHER EXPRESS OR IMPLIED WARRANTY OF FITNESS OR MERCHANTABILITY, and no agent of Bayer is authorized to do so except in writing with a specific reference to this warranty. Any damages arising from a breach of this warranty shall be limited to direct damages and shall not include consequential commercial damages such as loss of profits or values, etc.

EPA Est. 11556-DEU-I

EPA Reg. No. 11556-REI

Manufactured for Bayer HealthCare LLC
Animal Health Division
Shawnce Mission, Kansas 66201 USA

Supersedes: 07/10/07

(Label on Individual Tube)

Advantage® Plus 10

9.10% Imidacloprid

0.46% Pyriproxyfen

0.014 fl. oz. (0.4 mL)

EPA Reg. No. 11556-REI

CAUTION

Keep Out of Reach of Children

Read The Entire Label Before Use

BAYER

Lot No. 0000000



Doug Spilker <doug.spilker.b@bayer.com>

09/17/2007 05:19 PM

To Kable Davis/DC/USEPA/US@EPA

CC

bcc

Subject Revised Labels for Advantage Plus Dogs (File Symbols 11556-REI, -REL, - RET, - RGN)

Bo,

All the attached labels, text dated 09/17/07, have had minor corrections made to them, and are outlined in the table below. These draft labels replace those on file and pending review for File Symbols 11556- REI, -RET and - RGN.

Page	Change
1	Bullet 15 - removed "rapidly"
2	Bullet 5 - replaced "[(biting) (chewing)] lice," with "fleas" and
	reordered bullets, Replaced "In ert" with "Other" in active
	ingredient statement
3	Changed medical emergency number
4	Removed "only" from first bullet
5	Added "s" to infestation; "Inert" to "Other."
6	Changed medical emergency number
7	No changes
8	No changes
9	Added word "waterproof" in the shampooing/swimming
	statement, corrected STORAGE and DISPOSAL statement
	according to PR 2001-6; revised warranty statement per EPA
	request.
10	No changes

Please call if you have questions or wish to discuss these labels. best regards,

Doug

Doug Spilker Ph.D. Manager - EPA Reg. Affairs BAYER HEALTHCARE LLC ANIMAL HEALTH

Office: +1 913-268-2751 Mobile: +1 816-506-3102 Fax: +1 913-268-2135

Email: doug.spilker.b@bayer.com

Address: P.O. Box 390 Shawnee Mission, KS 66201-0390

Country: USA

Bayer Animal Health "Powered by People, Driven by Science"

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For alternale languages please go to http://bayerdisclaimer.bayerweb.com



AdvantagePlus100d.pdf AdvantagePlus10d.pdf AdvantagePlus20d.pdf AdvantagePlus55d.pdf

Bayer HealthCare Animal Health Division

BAYER BAYER E R

Via Federal Express

July 10, 2007

Document Processing Desk (NO REGFEE – Additional Information)
Office of Pesticide Programs (7504P)
U.S. Environmental Protection Agency
Room S-4900, One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202-4501

Attention:

Mr. Bo Davis - Registration Division

Subject:

Pending Applications for the Registration of Advantage[®] Plus 10, 20, 55, and 100 Products

(EPA File Symbols 11556-REI, REL, RET, and RGN) for pest control on dogs and Advantage[®] Plus 9 and 18

Products for pest control on cats (File Symbol

Nos. 11556-REA and 11556-REO)

Bayer HealthCare LLC Animal Health Division 12707 Shawnee Mission Parkway Shawnee Mission, KS 66216-1846

Dear Mr. Davis:

Pursuant to 40 CFR 157.34, "The registrant of a pesticide product required to be in child-resistant packaging shall certify to the Agency that the package meets the standards of § 157.32."

The subject pending applications for registration are for products which will be required to be in child-resistant packaging. Accordingly, please find enclosed with this cover letter six separate CRP certification letters for the respective subject products.

bille

If you have any questions, please do not hesitate to call me at (913) 268-2751.

Sincerely

Douglas A. Spilker. Ph. 16.

Manager, EPA Regulatory Affairs

Doug.Spilker.b@Bayer.com

DAS/lt

Enclosures: Six Certification Letters

Bayer HealthCare Animal Health Division



Via Federal Express

July 10, 2007

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Office of Pesticide Programs (7504P)
U.S. Environmental Protection Agency
Room S-4900, One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202-4501

Bayer HealthCare LLC Animal Health Division t2707 Shawnee Mission Parkway Shawnee Mission, KS 66216-1846

Attention: Mr. Bo Davis

Registration Division

Subject: Advantage® Plus 10 (EPA File Symbol 11556-REI)

Child-Resistant Packaging Certification

Dear Mr. Davis:

I certify that the packaging that will be used for this product meets the standard of 40 CFR 157.32.

Sincerely,

H. Lewy Mc Namara F. Terry McNamara

Director

Preclinical Development and EPA Regulatory Affairs

FTM:DAS/lt

CHILD-RESISTANT PACKAGING REVIEW Technical Review Branch

IN <u>0</u>	7/10/2007 OUT <u>08/6/2007</u>
RD, TRB, Reviewed by <u>Rosaliı</u>	Rosalena Ligioso nd L. Gross 08/6/2007
EPA Reg. No. or File Symbol 1	1556-REI
DP Barcode <u>D341440 see</u>	e also D338713
Decision # <u>215323</u> EPA Petition or EUP No	
Date Division Received 04/05/	2007
Type Product(s) <u>Insecticide (fl</u>	ea product)
.,	470894-00 (cover letter), 470894-07, 08, 09, 10 Note this data was submitted to cover EPA Reg No. 56-REA also
Product Mgr./Chemical Review Division <u>RD</u>	Mgr/Contact Person <u>RM 01 (Kable Davis)</u>
Product Name(s) <u>Advantage F</u>	Plus 10 for Dogs
Company Name(s) <u>Bayer Hea</u>	Ithcare LLC
to s	riew of 4 CRP studies to determine if they are adequate upport CRP certification for retail size of 4 and 6 tube ters of nonchild-resistant tubes (1ml size and 0.4ml fill el).
Active Ingredient(s), PC code,	& % Imidacloprid 9.1% Pyriproxyfen 0.46%

Summary of Findings

The child-resistant packaging, CRP, certification (July 10, 2007) submitted is acceptable. Child Study 4 tube blister 0.4 ml size (GLM 27022, MRID 470894-07) was a pass according to the child sequential test in 16 CFR 1700.20. Senior Adult Use Effectiveness, SAUE, Study 4 tube blister 0.4 ml size (GLM 27022, MRID 470894-08) was a pass of the Senior Adult test in 16 CFR 1700.20. Child Study 6 tube blister 0.4 ml size (GLM 27023, MRID 470894-09) was a pass according to the child sequential test in 16 CFR 1700.20. Senior Adult Use Effectiveness Study 6 tube blister 0.4 ml size (GLM 27023, MRID 470894-10) was a pass of the Senior Adult test in 16 CFR

1700.20.

In conclusion all the requirements for CRP have been met for this product. However, the directions on opening the package given to the senior during testing for the 4 and 6 tube blisters must be the same directions given to consumers. These directions are on the label for this product, which was dated July 10, 2007. Additionally, should any human experience/epidemiological evidence indicate a problem once the product is in the marketplace, the Agency reserves the right to question the child resistance of the package involved.

<u>Package</u>

The package is a plastic blister with a foil backing containing either 4 or 6 tubes of product. The blister is the child-resistant packaging not the individual tubes.

Toxicity

The toxicity of the product, which contains 9.1% Imidacloprid and 0.46% Pyriproxyfen, is based on toxicity data for a 9.1% Imidacloprid and 0.9% Pyriproxyfen formulation. The acute oral LD $_{50}$ was 1000mg/kg for the female rat and 1283mg/kg for the male rat per MRID 45096904. The female rat acute oral LD $_{50}$ 1000mg/kg was used for purposes of CRP. The toxic or harmful amount for an 11.4 kg child is 11.4g (1000mg/kg x 11.4kg), which is 10.4ml of product (11.4g divided by 1.092g/ml). For a tube with 0.4 ml of product a toxic or harmful amount is 26 tubes. For CRP testing a child failure is 9 tubes per 16 CFR 1700.20. Another acute oral LD $_{50}$ study MRID 470894-11 (9.0% Imidacloprid and 0.48% Pyriproxyfen) was submitted to confirm CRP was required for the product. This study indicates an acute oral LD $_{50}$ 1098mg/kg for the female rat, which means 12.5g or 11.4ml is a toxic or harmful amount for an 11.4kg child. Therefore a child failure remains 9 tubes per 16 CFR 1700.20.

Company Data

The company submitted a CRP certification and two Child-Resistant Effectiveness and two Senior Adult Use Effectiveness studies to demonstrate the 4 tube and 6 tube blister cards were child-resistant packaging.

Child Study 4 tube blister 0.4 ml size (GLM 27022, MRID 470894-07) involved giving each child 3 blister cards with 4 tubes (1 ml size tube) each containing 0.4 ml of water at the start of the test. A child failure was defined as access to 9 blister cavities as the blister card was the child-resistant feature. The results were one child failure.

Senior Adult Use Effectiveness Study 4 tube blister 0.4 ml size (GLM 27022, MRID 470894-08) involved having the test subjects open one blister cavity during a 5 minute test period and a one minute test period. Scissors were made available during testing. The results of the study were 100% SAUE.

Child Study 6 tube blister 0.4 ml size (GLM 27023, MRID 470894-09) involved giving each child 2 blister cards with 6 tubes (1 ml size tube) each containing 0.4 ml of water at the start of the test. A child failure was defined as access to 9 blister cavities as the blister card was the child-resistant feature. The results were no child failures.

Senior Adult Use Effectiveness Study 6 tube blister 0.4 ml size (GLM 27023, MRID 470894-10) involved having the test subjects open one blister cavity during a 5 minute test period and a one minute test period. Scissors were made available during testing. The results of the study were 99% SAUE.

Analysis of Data and Conclusion

The CRP certification (July 10, 2007) submitted is acceptable.

Child Study 4 tube blister 0.4 ml size (GLM 27022, MRID 470894-07) involved giving each child 3 blister cards with 4 tubes (1 ml size tube) each containing 0.4 ml of water at the start of the test. A child failure was defined as access to 9 blister cavities as the blister card was the child-resistant feature. The results were 1 child failure, which was a 51 month old male child that accessed 9 blister cavities. Additionally, one child accessed 4 blister cavities, two children accessed 2 blister cavities each, and three children accessed one blister cavity each. There was an error in calculating the age of one male child who was actually 52 months old and not 43 months old. However, the error will not effect the conclusion of the study, that the package is child-resistant. This study was a pass according to the child sequential test in 16 CFR 1700.20.

Senior Adult Use Effectiveness Study 4 tube blister 0.4 ml size (GLM 27022, MRID 470894-08) involved having the test subjects open one blister cavity during a 5 minute test period and a one minute test period. Scissors were made available during testing because the test directions given to the seniors called for the use of a cutting tool. The results of the study were 100% SAUE. There was an error in calculating the age of one female who was actual 62 years old and not 67 years old. However, the error will not effect the conclusion of the study that the package is SAUE. The study is a pass of the Senior Adult test in 16 CFR 1700.20.

Child Study 6 tube blister 0.4 ml size (GLM 27023, MRID 470894-9) involved giving each child 2 blister cards with 6 tubes (1 ml size tube) each containing 0.4 ml of water at the start of the test. A child failure was defined as access to 9 blister cavities as the blister card was the child-resistant feature. The results were no child failures, but one child accessed 3 blister cavities and two children accessed one blister cavity each. This study was a pass according to the child sequential test in 16 CFR 1700.20.

Senior Adult Use Effectiveness Study 6 tube blister 0.4 ml size (GLM 27023, MRID 470894-10) involved having the test subjects open one blister cavity during a 5 minute test period and a one minute test period. Scissors were made available during testing because the test directions given to the seniors called for the use of a pair of scissors. The results of the study were 99% SAUE, one 54 year old female failed during the one minute test period. There was an error in calculating the age of one female who was actual 53 years old and not 52 years old. However, the error will not effect the conclusion of the study that the package is SAUE. The study is a pass of the Senior Adult test in 16 CFR 1700.20.

In conclusion all the requirements for CRP have been met for this product. However, the directions on opening the package given to the senior during testing for the 4 and 6 tube blisters must be the same directions given to consumers. These directions are on the label for this product, which was dated July 10, 2007. Additionally, should any human experience/epidemiological evidence indicate a problem once the product is in the marketplace, the Agency reserves the right to question the child resistance of the package involved.

Bayer Studies for CR Blister with Tubes Chart

Imidacloprid 9.1% and Pyriproxyfen 0.46%

EPA#	Toxic/Harmful Amt	Child Failure	ml in tube	4 tub	e blister	6 tube	blister	CRP Data	CRP Cert
	1			SAUE	CRE	SAUE	CRE	,	
11556-REL	Acute oral LD ₅₀ = 1098 mg/kg female rat D338715 EPA Reg No 11556-REA MRID 470894-11 July 2007. Toxic/harmful amount 11.4 kg child = 12.5g=11.4ml	9 tubes	1	100%	0 Fail	99%	0 Fail	Yes	Ok
11556-REA	Acute oral LD ₅₀ = 1098 mg/kg female rat D338715 EPA Reg No 11556-REA MRID 470894-11 July 2007. Toxic/harmful amount 11.4 kg child = 12.5g=11.4ml	9 tubes	0.4	100%	1 Fail	99%	0 Fail	Yes	Ok
11556-REO	Acute oral LD _{so} = 1098 mg/kg female rat D338715 EPA Reg No 11556-REA MRID 470894-11 July 2007. Toxic/harmful amount 11.4 kg child = 12.5g=11.4ml	9 tubes	0.8	Pass	Pass	Pass	Pass	use REL and REA Data	Ok

Bayer HealthCare Animal Health Division



015

Via Federal Express

July 10, 2007

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Office of Pesticide Programs (7504P)
U.S. Environmental Protection Agency
Room S-4900, One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202-4501

Bayer HealthCare LLC Animal Health Division 12707 Shawnee Mission Parkway Shawnee Mission, KS 66216-1846

Attention:

Mr. Bo Davis

Registration Division

Subject:

Advantage® Plus 10 (EPA File Symbol 11556-REI)

Child-Resistant Packaging Certification

Dear Mr. Davis:

I certify that the packaging that will be used for this product meets the standard of 40 CFR 157.32.

Sincerely,

Tr. Levy Mc Namara
F. Terry Mc Namara

Director

Preclinical Development and EPA Regulatory Affairs

FTM:DAS/lt

EFFICACY REVIEW

PRODUCT: Advantage Plus 10 for Dogs, Advantage Plus 20 for Dogs,

Advantage Plus 55 for Dogs, Advantage Plus 100 for Dogs

FILE SYMBOL: 11556-RE1, 11556-REL, 11556-RET, 11556-RGN

DATE: August 6, 2007

DP BARCODE: D342416, D342417, D342418, D342419

DECISION NUMBER: 215323, 215314, 215321, 215493

GLP: No

CHEMICAL: Imidacloprid (9.1%)

CHEMICAL NUMBER: 129099

PURPOSE: Review data to support the addition of dog lice

(Trichodectes canis)

MRID: 47190401. Doyle, J., Egan, T. (2006) A Controlled

Randomised Study to Evaluate the Efficacy of Advantage Against a Natural Infestation of Dog Lice (Trichodectes canis) Following a Single Topical Administration to Adult Mixed Breed Dogs: Final Study Report. Project Number: 144/914, 75950. Unpublished study prepared by Charles

River Laboratories BioLabs Europe. 130p.

TEAM REVIEWER: Kable Bo Davis

EFFICACY REVIEWER: Kable Bo Davis, M.S., Entomologist

SECONDARY

EFFICACY REVIEWER: Joanne Edwards, M.S., Entomologist

BACKGROUND:

Advantage Plus 10, Advantage 20, Advantage 55 and Advantage 100 are ready-to-use spot on treatments for dogs intended for the month long control of fleas and lice. The proposed labels contained the following label claims concerning lice:

- 1. Once-A-Month Topical Treatment for Fleas and Lice
- 2. Kills [(biting) (chewing)] lice
- 3. Kills [(biting) (chewing) lice, which may serve as intermediate hosts for tapeworms (*Dipylidium caninum*)
- 4. Kills [(biting) (chewing)] lice and prevents further infestations

DATA REVIEW:

The following data review is comprised of explanations of materials and methods, and a summation of experimental results containing tables with reformatted data.

47190401. Doyle, J., Egan, T. (2006) A Controlled Randomised Study to Evaluate the Efficacy of Advantage Against a Natural Infestation of Dog Lice (Trichodectes canis) Following a Single Topical Administration to Adult Mixed Breed Dogs: Final Study Report. Project Number: 144/914, 75950. Unpublished study prepared by Charles River Laboratories BioLabs Europe. 130p.

The experimental design consisted of separating 20 dogs into two groups of ten containing both males and females. All dogs included in the study were naturally infested with dog lice (*Trichodectes canis*) and had a minimum of 10 infesting lice. Group 1 acted as a control, while dogs within the second group were treated (via spot treatment) with 0.1 mL/kg bodyweight of Advantage on day 0. Obscrvations on efficacy were taken on days 1, 2, 7, 14, 21, 28 and 36.

Results:

Table 1. Lice Counts

Group	Animal	Total Number of Lice								
		Day -	Day-	Day						
		7	3	1	2	7	14	21	28	36
	1	-	52	-	86	92	52	52	95	68
	2	-	1	77		66	63	72		90
	3	21	29	54	9	3	0	0	0	0
	4	20	80	13	15	1	0	0	0	0
Control	5.	85	44	61	88	64	49	81	85	44
	6	79	36	53	-	80	76	57	83	89
*	7		70	61	88	66	59	97	99	81
1	8	31	37	32	46	37	16	13	25	42
	9	+		-		99	94	91	75	
	10	4	72		-	95	65	65	69	49
	4									
	1	36	29	3	0	0	0	0	0	0
	2	-	67	1	0	0	0	0	0	0
	3		74	4	5	0	2	0	0	0
	4		96	16	10	0	0	0	0	0
Treatment	5	-	91	20	6	0	0	0	0	0
	6 :	-	-	68	13	0	0	0	0	0
	7	59	47	0	0	0	0	0	0	0
	8	-	42	22	0	0	0	0	0	0
]	9.	73	41	1	0	0	0	0	0	0
	10	41	35	4	0	0	0	0	0	0

Table 2. Efficacy Results

Day	% Efficacy (mean)
1	91%
2	98%
7	100%
14	100%
21	100%
28	100%
36	100%

The percent efficacy ranged from 91% (1 day) to 100% (days 7-36).

RECOMMENDATIONS:

The submitted data support the addition of biting or chewing lice to products: 11556-REI, 11556-REL, 11556-RET and 11556-RGN. The following recommendation applies:

1. Revise the label claim "Kills [(biting) (chewing) lice, which may serve as intermediate hosts for tapeworms (<u>Dipylidium caninum</u>)" to read "Kills fleas, which may serve as intermediate hosts for tapeworms".

			· ·	Print Form
Please read instructions an reverse before con	pleting form.	Form Ap	ad. OMB No. 207	O-0060. Approval expires 2-28-
SEPA Environmen	United States tal Protecti shington, OC 20		× Registration Amendme Other	
420	Applicati	on for Pesticide - Sec	tion I	
t. Company/Product Number 11556-REI		2. EPA Product Ma Tom Harris	negar	3. Proposed Classification None Restricted
4. Company/Product (Name) Advantage Plus 10 for Dogs		PM# Acting PM1		- None nesthered
5. Neme end Address of Applicant IInclude ZIP Bayer HealthCare LLC, Animal Health Divi P.O. Box 390 Shawnee Mission, KS 66201-0390 Check if this is a new address		(b)lil, my product to:		e with FIFRA Section 3(c)[3) I in composition and labeling
		Section - II		
Amondment - Explain below. Resubmission in rosponse to Agency let Notification - Explain below. Explanation: Use edditional pegalst if neces Non-fast Track Amandment (review of dat Although this action is pending & should be	sary. 1For sections); Proposed fe	Agency let "Mo Too" Nother - Expon 1 and Section !!.!	Application. plain below. Action: Modification	of the Label. Justification:
		Section - III		_
1. Meterial This Product Will Be Peckaged In:		0000000		
Child-Resistent Peckaging X Yes Yes X No * Certification must be submitted Unit Peckaging If "Yes" Unit Packaging w	No. per	Water Soluble Packaging Yos X Noxt If "Yes" No. per Package wgt contains	X P	ntainer Motel Yeetic Glass Paper Othor (Specify)
3. Location of Not Contents Information X Label Container	1	atail Container 1/6-0.4 mL tubes	5. Location of Lebel 1 On Label On Labeling	Directions accompaning product
6. Manner in Which Label is Affixed to Product	Litho Pepe Sten	graph X Other	See attachmen	t
		Section - IV		
t. Contact Point Complete items directly belo	w for identificati		, if necossary, to proce	ss this application.)
Name Douglas A. Spilker (doug.spilker.b@bayer.c	com)	Title EPA Regulatory Manager		lephone No. (Indude Area Code) 3-268-2751 00
I certify that the statements I have made I ecknowledge that any knowlinglly felse both under epplicable law.	Certific on this form en- or misleading st	d all attachments thereto are tru	io, accureto and compli fine or imprisonment.co ແລະເຄດ	(Stamped) ن ځ
2. Signeture G. Mc Marnasa for Down	ulas Soilkar	3. Title EPA Regulatory Manager		
4. Typed Name	<i>J</i>	5. Dete		1 1
Douglas A Spiller		March 8 2007		

Bayer HealthCare Animal Health Division



470892-00

Via Federal Express

March 8, 2007

Document Processing Desk (REGFEE)
Office of Pesticide Programs (7504P)
U.S. Environmental Protection Agency
Room S-4900, One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202-4501

Attention:

Mr. Tom Harris

Registration Division

Subject:

Pending Applications for the Registration of

Advantage Plus 10, 20, 55, and 100 Products (EPA File Symbols 11556-REI, REL, RET, and RGN)

for pest control on dogs and Advantage[®] Plus 9 and 18

Products for pest control on cats (File Symbol

Nos. 11556-REA and 11556-REO)

Dear Mr. Harris:

Enclosed with this cover letter are revised draft labeling with appropriate supporting documents for the pending registrations of Bayer's Advantage® Plus products for pest control on cats (EPA Files Symbols 11556-REA, and 11556-REO), and dogs (EPA File Symbols 11556-REI, 11556-REL, 11556-RET, and 11556-RGN). The purpose of this cover letter is to provide an explanatory overview of the submission which may aid in the processing of the enclosed information and respective applications.

The time of the original submission, April 10, 2000, predates PRIA and as pending actions should be "grandfathered." However, we agree to make all six related actions Vol-Pay Actions, and we will pay the appropriate fees.

Bayer HealthCare LLC Animal Health Division 12707 Shawnee Mission Parkway Shawnee Mission, KS 66216-1846

Page 2 March 8, 2

Briefly, the most significant item previously preventing the registrations was that the products had to be in Child-Resistant Packaging (CRP). The packaging scheme for all six registrations is similar, and the CRP testing data for the various sizes are enclosed. The testing design to satisfy the requirements for all product presentations was developed with the agreement of the Agency's expert, Dr. Rosalind Gross. In addition, to support a 9-week kitten label, the reports on three kitten studies and an overall summary (included in the two kitten/cat product applications) are enclosed. These items are discussed in more detail later.

On April 10, 2000, Bayer HealthCare LLC, Animal Health Division submitted draft labels and appropriate documents for the subject registration actions. The Agency reviewed these documents and responded on a number of items, such as requiring the products to be marketed in Child-Resistant Packaging (CRP). Bayer responded to some of the items, but did not on others. We acknowledge that there has been quite a lag in activity with this action, mostly due to changing marketing focus, and the need to generate Child-Resistant Packaging. However, Bayer Healthcare has renewed interest in these products, and the enclosed and accompanying information is in reply to the Agency's comments and/or to support proposed revisions to the pending actions.

The insecticide formulation is identical for all six products. The six application/products differ in terms of use directions for cats or dogs and/or different dose/container sizes for different sizes of cats and dogs. All of the products control one pest - fleas. These products are similar to the Advantage products (Advantage® 9, EPA Reg. No. 11556-116; Advantage® 18, EPA Reg. No. 11556-118; Advantage® 10, EPA Reg. No. 11556-117; Advantage® 20, EPA Reg. No. 11556-119; Advantage® 55, EPA Reg. No. 11556-120; and Advantage® 100, EPA Reg. No. 11556-122), except a small amount (0.46%) of a very effective insect growth regulator, pyriproxyfen, has been added to enhance efficacy against flea eggs. Whereas Advantage® was efficacious against larval and adult fleas, the new combination product is effective against flea larvae, adult fleas, and flea eggs.

The method of application is the same for all six products and is the same application method as for the currently registered Advantage[®] products. The insecticide formulation is applied from an individual tube to dogs or

Mr. Tom Harris
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Office of Pesticide Programs (7504P)
U.S. Environmental Protection Agency

Page 3 March 8, 2007

cats to a localized area on the skin between the shoulders or on the neck to control fleas. For large dogs, application to a couple of localized areas along the neck and back is recommended. This is the same as for Bayer's currently registered Advantage[®] products (EPA Reg. Nos. 11556-116, -117, -118, -119, -120, -122).

Specifically, there are two pending registration applications for products to control fleas on cats. One product, Advantage® Plus 9, will treat cats 9 lbs. or less in size. The dose for this product is 0.4 mL of solution in a plastic tube. The other product for cats - Advantage® Plus 18 - will treat cats greater than 9 lbs. in size. The dose size for this product is 0.8 mL of solution in a plastic tube.

There are four registration applications for products to control fleas on dogs. Advantage® Plus 10 will treat small dogs and puppies which are 10 lbs. or less in size. The dose size for this product is 0.4 mL of solution in a plastic tube. Advantage Plus® 20 will treat dogs 11 to 20 lbs. in size. The dose size for this product is 1.0 mL. Advantage® Plus 55 will treat dogs which are larger than 20 lbs. in size, but less than 55 lbs. The dose size for this product is 2.5 mL. Advantage® Plus 100 is for dogs greater than 55 lbs. in size. The dose size for this product is 4.0 mL.

The different product names, EPA File Symbol, animals (dog or cat), animal sizes, tube sizes and number of tubes per package are also shown in the attached table for ease of reference.

The packaging for the cat products will be identical to the packaging used with the currently registered Advantage® products for cats (EPA Reg. Nos. 11556-116 and -118) except the tubes will be in a Child-Resistant blister (discussed later). The packaging for the cat products will consist of a cardboard box with all appropriate label text except for the directions for use. Inside the box will be a leaflet containing all the label text. Also inside the box will be a CRP blister package containing 4 or 6 tubes of the appropriate size. Please note, the Advantage® Plus products will be marketed in either a 4-tube or a 6-tube package just as the currently registered Advantage® products are sold in 4-tube and 6-tube package sizes.

The packaging for the dog products will also consist of the same type of CRP blister pack placed in a small carton containing 4 or 6 tubes of the

Mr. Tom Harris
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Office of Pesticide Programs (7504P)
U.S. Environmental Protection Agency

Page 4 (Marcli 8, 2007

appropriate size. As with the cat products, the outer cardboard box will contain all the appropriate labeling except for directions for use. A leaflet with the complete label text will be inside the box with the appropriate blister package. The presentations are identical as for Bayer's currently registered Advantage® products for dogs (EPA Reg. Nos. 11556-117, -119, -120, -122).

The plan for the packaging has not changed from the original submission of 4/1/2000, except that the blister package has been changed to meet child-resistant packaging standards.

In the previous applications for Advantage[®] Plus 9 for Cats and Kittens (EPA File Symbol 11556-REA) and for Advantage[®] Plus 18 for Cats (EPA File Symbol 11556-REO) Bayer did not submit domestic animal safety data for kittens. At the time of submission these studies were underway and being discussed with Agency representatives (cited in the enclosed applications). All of these studies are complete. There are three studies described in 1) Bayer Report No. 75120 with a report amendment – Bayer Report No. 75120-1; 2) Bayer Report No. 75190 with a report amendment – Bayer Report No. 75190-1; and 3) Bayer Report No. 75191 with a report amendment – Bayer Report No. 75191-1. These three kitten safety studies with the report amendments support a 9-week kitten age restriction. The reports and their amendments are included with the application for Advantage[®] Plus 9 for Cats and Kittens (EPA File Symbol 11556-REA), but the data also support the same label restriction for the Advantage[®] Plus 18 for Cats (EPA File Symbol 11556-REO).

As earlier related, the insecticide formulation is the same for all six products. Also because the acute toxicity value for the formulation was below the 1500 mg/kg "trigger," and because this is a residential use, the products must be marketed in Child-Resistant Packaging (CRP). To resolve this issue for all six products including that each product is to be marketed in two different presentations – a 4-tube package and a 6-tube package – Bayer representatives, Great Lakes Marketing (a CRP testing facility which Bayer has contracted) and Agency representatives, primarily Dr. Rosalind Gross, have had numerous discussions and meetings. The end results of these efforts are Bayer has developed CRP blister packaging for all tube and dose sizes including both 4-tube blisters and 6-tube blisters for each size. Sixteen reports detailing the CRP testing of these blisters are enclosed in this submission.

Page 5 (March 8, 2007

In agreement with Dr. Rosalind Gross, for the largest dog size, Advantage® Plus 100 (EPA File Symbol 11556-RGN) with a 4.0 mL dose size, Great Lakes Marketing (GLM) tested both the 4-tube and 6-tube blisters with this size tube filled with 4.0 mL of water. The four reports on this testing — 4.0 mL x 4-tube blister child testing (Bayer Report No. 75909), 4.0 mL x 4-tube blister senior testing (Bayer Report No. 75910), 4.0 mL x 6-tube blister child testing (Bayer Report No. 75911), and 4.0 mL x 6-tube blister senior testing (Bayer Report No. 75912) — are enclosed with the documents for Advantage® Plus 100. No other data are included with this particular application.

In agreement with Dr. Rosalind Gross, for Advantage[®] Plus 55 (EPA File Symbol 11556-RET) with a 2.5 mL dose size, GLM tested both 4-tube and 6-tube blisters with this size tube filled with 2.5 mL of water. The four reports on this testing – 2.5 mL x 4-tube blister child testing (Bayer Report No. 75905), 2.5 mL x 4-tube blister senior testing (Bayer Report No. 75906), 2.5 mL x 6-tube blister child testing (Bayer Report No. 75907), and 2.5 mL x 6-tube blister senior testing (Bayer Report No. 75908) – are enclosed with the documents for Advantage[®] Plus 55. No other data are included with this particular application.

As the dose size for Advantage® Plus 9 for Cats and Kittens (EPA File Symbol 11556-REA) and the dose size for Advantage® Plus 10 for Dogs and Puppies (EPA File Symbol 11556-REI) are the same - 0.4 mL packaged in the 1 mL tubes in the same blisters (including 4-tube and 6-tube blisters), Dr. Rosalind Gross agreed testing these I mL tubes filled with 0.4 mL water in 4-tube blisters and 6-tube blisters would satisfy the requirements for both the Advantage® Plus 9 for Cats and the Advantage® Plus 10 for Dogs and Puppies registrations. GLM tested these 4-tube and 6-tube blisters. The four reports on this testing - 0.4 mL in 1 mL tubes x 4-tube blister child testing (Bayer Report No. 75913), 0.4 mL in 1 mL tubes x 4-tube blister senior testing (Bayer Report No. 75914), 0.4 mL in I mL tubes x 6-tube blister child testing (Bayer Report No. 75915), and 0.4 mL in 1 mL tubes x 6-tube blister senior testing (Bayer Report No. 75916) – are included with the Advantage[®] Plus 9 for Cats and Kittens application, but they also support the registration of Advantage® Plus 10 for Dogs and Puppies.

Mr. Tom Harris
Document Processing L & (REGFEE)
Office of Pesticide Programs (7504P)
U.S. Environmental Protection Agency

Page 7 (March 8, 2007

I hope this overview cover letter is helpful in processing the attached applications. If you have any questions, please do not hesitate to call me at (913) 268-2751.

J. J. Mc namara for Douglas Spilker

Sincerely,

Douglas A. Spilker. Ph. D.

Manager, EPA Regulatory Affairs

Doug.Spilker.b@Bayer.com

DAS/lt

Enclosures

Transmittal Document

Name and Address of Submitter
 Bayer HealthCare LLC
 Animal Health Division
 Box 390
 Shawnee Mission, Kansas 66201-0390

F.J. McNamara for Douglas Spilker

Douglas A. Spilker, Ph.D. Manager, EPA Regulatory Affairs (913) 268-2751

- 2. Regulatory Action in Which this Package is Submitted

 Data submitted to support proposed label claim for Advantage® Plus 55 for Dogs
 (EPA File Symbol 11556-RET)
- 3. <u>Transmittal Date</u> March 8, 2007
- 4. <u>List of Submitted Studies</u>:

MRID No.	Volume	
47089201	1 -	"Child-Resistant Packaging (CRP) Child Panel Test of 4 x 2.5 mL Advantage® Plus Blisters for Dogs," 40 CFR Part 157.20 and 16 CFR Part 1700.20, Bayer Report No. 75905, L. M. Dixon, 58 p.
47089202	2 -	"Child-Resistant Packaging (CRP) Senior Adult Panel Test of 4 x 2.5 mL Advantage® Plus PVC Blisters for Dogs," 40 CFR Part 157.20 and 16 CFR Part 1700.20, Bayer Report No. 75906, L. M. Dixon, 241 p.
47089203	3 -	"Child-Resistant Packaging (CRP) Child Panel Test of 6 x 2.5 ml Advantage® Plus for Dogs," 40 CFR Part 157.20 and 16 CFR Part 1700.20, Bayer Report No. 75907, L. M. Dixon, 57 p.
47089204	4 -	"Child-Resistant Packaging (CRP) Senior Adult Panel Test of 6 x 2.5 mL Advantage® Plus PVC Blisters for Dogs," 40 CFR Part 157.20 and 16 CFR Part 1700.20, Bayer Report No. 75908, L. M. Dixon, 238 p.

Document Processing Desk (REGFEE) Office of Pesticide Programs (7504P) U.S. Environmental Protection Agency Room S-4900, One Potomac Yard 2777 South Crystal Drive Arlington, VA 22202-4501

Attachments:

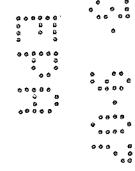
Letter to Mr. Tom Harris

Application for Pesticide Registration - Advantage Plus 9 for Cats

- 5 copies draft label 4-pack
- 5 copies draft label 6-pack
- 1 copy Letter of Authorization from MGK
- 1 copy Letter of Authorization from Bayer
- 1 copy data matrix
- 1 copy public data matrix
- 2 copies Confidential Statement of Formula
- 3 copies data transmittal document
- 3 copies Bayer Report No. 75922 (Acute Oral Toxicity)
- 3 copies Bayer Report No. 75120 (Domestic Animal Safety Kittens)
- 3 copies Bayer Report No. 75120-1 (Domestic Animal Safety Kittens)
- 3 copies Bayer Report No. 75190 (Domestic Animal Safety Kittens)
- 3 copies Bayer Report No. 75190-1 (Domestic Animal Safety Kittens)
- 3 copies Bayer Report No. 75191 (Domestic Animal Safety Kittens)
- 3 copies Bayer Report No.75191-1 (Domestic Animal Safety Kittens)
- 3 copies Bayer Report No. 75913 (Child Resistant Packaging Study)
- 3 copies Bayer Report No. 75914 (Child Resistant Packaging Study)
- 3 copies Bayer Report No. 75915 (Child Resistant Packaging Study)
- 3 copies Bayer Report No. 75916 (Child Resistant Packaging Study)

Application for Pesticide Registration - Advantage Plus 18 for Cats

- 5 copies draft label 4-pack
- 5 copies draft label 6-pack
- 2 copies Confidential Statement of Formula
- 1 copy Letter of Authorization from MGK
- 1 copy Letter of Authorization from Bayer



X::moiij/AdvantagePlusSubmission/EPA AdvantagePlus2007Mar das ltr.doc

Application for Pesticide Registration - Advantage Plus 10 for Dogs 5 copies draft label 4-pack 5 copies draft label 6-pack 1 copy Letter of Authorization from MGK 1 copy Letter of Authorization from Bayer 1 copy data matrix 1 copy public data matrix 2 copies of Confidential Statement of Formula 3 copies data transmittal document Application for Pesticide Registration - Advantage Plus 20 for Dogs 5 copies draft label 4-pack 5 copies draft label 6-pack 1 copy Letter of Authorization from MGK 1 copy Letter of Authorization from Bayer 2 copies Confidential Statement of Formula 3 copies Bayer Report No. 75897 (Child Resistant Packaging Study) 3 copies Bayer Report No. 75898 (Child Resistant Packaging Study) 3 copies Bayer Report No. 75893 (Child Resistant Packaging Study) 3 copies Bayer Report No. 75894 (Child Resistant Packaging Study) Application for Pesticide Registration – Advantage Plus 55 for Dogs 5 copies draft label 4-pack 5 copies draft label 6-pack 2 copies of Confidential Statement of Formula 1 copy Letter of Authorization from MGK 1 copy Letter of Authorization from Bayer 3 copies Bayer Report No. 75905 (Child Resistant Packaging Study) 3 copies Bayer Report No. 75906 (Child Resistant Packaging Study) 3 copies Bayer Report No. 75907 (Child Resistant Packaging Study) 3 copies Bayer Report No. 75908 (Child Resistant Packaging Study) Application for Pesticide Registration – Advantage Plus 100 for Dogs 5 copies draft label 4-pack 5 copies draft label 6-pack 2 copies Confidential Statement of Formula 1 copy Letter of Authorization from MGK 1 copy Letter of Authorization from Bayer 3 copies Bayer Report No. 75909 (Child Resistant Packaging Study) 3 copies Bayer Report No. 75910 (Child Resistant Packaging Study) 3 copies Bayer Report No. 75911 (Child Resistant Packaging Study)

3 copies Bayer Report No. 75912 (Child Resistant Packaging Study)



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY 1200 Pennsylvania Avenue, N.W. WASHINGTON, D.C. 20460

WASHINGTON, D.C. 20460							
Paperwork Reduction Act Notice: The public reporting burden for this collection of information is estimated to average 1.25 hours per response for registration and 0.25 hours per response for reregistration and special review activities, including time for reading the instructions and completing the necessary forms. Send comments regarding burden estimate or any other aspect of this collection of information, including suggestions for reducing the burden to: Director, Collection Strategies Division (2822T), U.S. Environmental Protection Agency, 1200 Pennsylvania Avenue, N.W., Washington, DC 20460. Do not send the completed form to this address.							
Certification with Respect to	Citation of Data						
Applicant's/Registrant's Name, Address, and Telephone Number Bayer HealthCare LLC, Animal Health Div, POB 390, Shawnee Mission, KS 662	01 (913-268-2751)	EPA Registration Number/File Symbol 11556-REI					
Active Incredients) and/or representative test compound(s) pyrlproxyfen, imidacloprid		Dale September 14, 2007					
General Use Pattem(s) (list_all those claimed for this product using 40 CFR Part 1) Indoor, Non-food	58)	Product Name Advantage Plus 10 for Dogs					
NOTE: If your product is a 100% repackaging of another purchased EPA-registe submit this form. You must submit the Formulator's Exemption Statement (EPA Formulator's EPA Form		or all the same uses on your labet, you do not need to					
I am responding to a Data-Call-In Notice, and have included with this form be used for this purposel.	a list of companies s	ent offers of compensation (the Data Matrix form should					
SECTION 1: METHOD OF DATA SUI	PPORT (Check one m	nethod only)					
l am using the cite-all method of support, and have included with this form a list of companies sent offers of compensation (the Data Matrix form should be used for this purpose).	under the	g the selective method of support (or cite-all option e selective method), and have included with this form a d list of data requirements (the Date Matrix form must be					
SECTION 11: GENERA	L OFFER TO PAY						
Required if using the cite-all method or when using the cite-all option under the sel		•					
SECTION III: CER	TIFICATION						
I certify that this application for registration, this form for reregistration, or this Data-Call-in response is supported by all data submitted or cited in the application for registration, the form for reregistration, or the Data-Call-in tesponse. In addition, if the cite-atl option or cite-all option under the selective method is indicated in Section I, this application is supported by all data in the Agency's files that (1) concern the properties or effects of this product or an identical or substantially similar product, or one or more of the ingredients in this product; and (2) is a type of data that would be required to be submitted under the data requirements in effect on the date of approval of this application if the application sought the initial registration of a product of identical or similar composition and uses.							
I certify that for each exclusive use study cited in support of this registration the written permission of the original data submitter to cite that study.	on or reregistration, th	at tam the original data submitter or that I have obtained					
I certify that for each study cited in support of this registration or reregistration that is not an exclusive use study, either: (a) I am the original data submitter; (b) I have obtained the permission of the original data submitter to use the study in support of this application; (c) all periods of eligibility for compensation have expired for the study; (d) the study is in the public titerature; or (e) thave notified in writing the company that submitted the study and have offered (l) to pay compensation to the extent required by sections 3(c)(1)(F) and/or 3(c)(2)(B) of FIFRA; and (ii) to commence negotiations to determine the amount and terms of compensation, if any, to be paid for the use of the study.							
t certify that in all instances where an offer of compensation is required, copies of all offers to pay compensation and evidence of their delivery in accordance with sections 3(c)(1)(F) and/or 3(c)(2)(B) of FIFRA are available and will be submitted to the Agency upon request. Should I fail to produce such evidence to the Agency upon request, I understand that the Agency may initiate action to deny, cancel or suspend the registration of my product in conformity with FIFRA.							
t certify that the stalements t have made on this form and all attach knowingly false or misleading statement may be punishable by fine or Impris							
Signature Wolfes A. Spille	Date 09/14/2007	Typed or Printed Name and Title Douglas A. Sptlker, EPA Reg. Affairs Manager					

EPA Form 8570-34 (12-2003) Electronic and Paper versions available. Submit only Paper version.

Product ingredient source information may be entitled to confidential treatment

Form appro	oved. OMB No. 2070-0060, 2070-0057, 2070	2-0107, 2070-0122, 2070-0164.
\$EPA		
Envi	United States	
	Washington, DC 20460	
Formula	tor's Exemption Statement	
	(40 CFR 152.85)	
Applicant's Name and Address	EPA File Symbol/Registra	ation Number
Bayer HealthCare LLC	11556-REI	
Animal Health Division	Product Name	
P.O. Box 390	Advantage Plus 1	0 for Dogs
Shawnee Mission, KS 66201		
		ement of Formula (EPA Form 8570-4)
	03/08/2007	
As an authorized representative of the applicant for registral	tion of the product Identified above, I certify	lhal:
(1) This product contains the following active ingredient(s):	
ny win way y fan		
pyriproxyfen	Evenntian for this active incres	lient)
imidacloprid (not citing Formulator's	exemption for this active ingred	nem)
(2) Of these, each active ingredient listed in paragraph (formulation or repackaging another product which co us from another person and meets the requirements	ntains that active ingredient, which is registe	of that active ingredient in the manufacturing, ered under FIFRA Section 3, is purchased by
(3) Indicate by checking (A) or (B) below which paragrap	on applies:	
(A) An accurate Confidential Statement of Formula (E	PA FORM 8570-4) for the above identified :	product is attached to this statement.
That formula statement indicates, by company name,	•	
paragraph (1).		
	OR	
기 (B) The Confidential Statement of Formula (CSF)(6	FPA Form 6570-4) referenced above and o	n lile with the EPA is complete, current, an
accurate and contains the information required on the		
	,	
(4) The following active ingredients in this product qualify	for the formulator's exemption.	
	Source	
Active Ingredient	Product Name	Registration Number
pyriproxyfen		
		

D.A. Spilker, EPA Reg. Affairs Mgr. 09/14/2007

Date

Copy 1 – EPA Copy 2 - Applicant copy



Approved OMB No. 2070-0060

		DATA MATRIX	
Dale: September 14, 2007	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	EPA Reg No./File Symbol: 11556-REL 11556-REL 11556-RET 11556-RGN	Page 1 of 11
Bayer Health Care LLC Animal Health Division P.O. Box 390 Shawnee Mission, KS 66201-0390		: Product: Advantage® Plus 10 for Dogs Advantage® Plus 20 for Dogs	Ingredient: Imidacioprid, CAS = 138261-41-3 Pyriproxyfen, CA5 = 95737-68-1
Guideline Study Name Reference Number	MRID Number	Submitter Status Note Report Number	Description

roduct Chemi	stry, Section 158.240	-				
		42055302	264	PER	BR 1759 (TGAI)	
		43306001	264	PER	BR 1879 (TGAI)	
61-1	Chemical identity	42256302	264	PER	BR 1766 (Formulation)	
		42055302	264	PER	BR 1759 (TGA1)	
	ļ	43306001	264	PER	BR 1879 (TGAI)	,
		42270801	264	PER	BR 1785 (TGAI)	
61-2	Statement of Composition	42256302	264	PER	BR 1766 (Formulation)	
	`	42055302	264	PER	BR 1759 (TGAI)	
61-3	Formation of impurities	42256302	264	PER	BR 1766 (Formulation)	
		42055303	264	PER	BR 1760 (TGAI)	
		43306002	264	PER	BR 1880 (TGAI)	
		42270802	264	PER	BR 1786 (TGAI)	
62-1	Preliminary analysis	42256302	264	PER	BR 1766 (Formulation)	
		. 42055303	264	PER	BR 1760 (TGA!)	
		43306002	264	PER	BR 1880 (TGAI)	
62-2	Certification of limits	42256302	264	PER	BR t766 (Formulation)	
	,	42055303	264	PER	BR 1760 (TGAI)	
	'	43213001	264	PER	BR 1874 (TGAI)	
		43306002	264	PER	BR 1880 (TGAI)	
		42256302	264	PER	BR 1766 (Formulation)	
62-3	Analytical method	4509690t	11556	OWN	Report No. 75130	Submitted with application for Advantage Plus 9 for Cats



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20460. Do not s	end the form to the address.			N		
<u> </u>	12.0007		DATA	MATRIX		
Bayer Health Care LLC Animal Health Division P.O. Box 390 Shawnee Mission, KS 66201-0390 Guideline Reference Number Guideline Study Name MRID Number 42055304 63-1 Chemical and Physical Properties 42256302			EPA Reg No	JFile Symbo	i: 11556-REL 11556-REL 11556-RET, 11556-RGN	Page 2 of 11
			Product: A A A	dvantage® Pl	us 10 for Dogs us 20 for Dogs lus 55 for Dogs lus 100 for Dogs	Ingredient: Imidaclopnid, CAS = 138261-41-3 Pyriproxyfen, CAS = 95737-68-1
Guideline Reference Number	Guideline Study Name	MRID Number	Submilter	Status	Note Report Number	Description
	<u> </u>	42055304	264	PER	BR 1761 (TGAI)	
63-1	Chemical and Physical Properties	42256302	264	PER	BR 1766 (Formulation)	
		42055304	264	PER	BR 1761 (TGAI)	
63-2	Appearance	42256302	264	PER	BR 1766 (Formulation)	
		42055304	264	PER	BR 1761 (TGAI)	
63-3	Physical state	42256302	264	PER	BR 1766 (Formulation)	
		42055304	264	PER	BR 1761 (TGAI)	
631	Odor	42256302	264	PER	BR 1766 (Formulation)	
63-5	Melting point	42055304	264	PER	BR 1761 (TGAI)	
63-6	Boiling point	42055304	264	PER	BR 1761(TGAI)	
		42055304	264	PER	BR 1761 (TGAI)	
63-7	Density	43356302	264	PER	BR 1761 (Formulation)	
63-8	Solubility	42055304	264	PER	BR 1761 (TGAI)	·
63-9	Vapor pressure	42055304	264	PER	BR 1761 (TGAI)	
63-10	Dissociation constant					N.A Does not dissociate
63-11	Octanol / water partition	42055304	264	PER	BR 1761 (TGAI)	
		42055304	264	PER	BR 1761 (TGAI)	
63-12	pH	42256302	264	PER	BR 1766 (Formulation)	
63-13	Stability	42055304	264	PER	BR 1761 (TGAI)	
63-14	Oxidizing / reducing action		264	PER		N.A No oxidative or reductive characteristics
63-15	Flammability	42055304	264	PER	BR 1761 (TGAT)	
63-16	Explodability	42055304	264	PER	BR 1761 (TGAI)	



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				DATA MATR	X		
Date: September 14, 2007		-	-	EPA Reg No File Sy	mbol: 11556-REL 11556-REL 11556-RET, 11556-RGN		Page 3 of 1J
Bayer Health Care LLC Animal Health Division P.O. Box 390 Shawnee Mission, KS 66201-03	00			Advantage	® Plus 10 for Dogs ® Plus 20 for Dogs ® Plus 55 for Dogs ® Plus 100 for Dogs		Ingredient: Imidacioprid, CAS = 138261-41-3 Pyriproxyfen, CAS = 95737-68-1
Guideline Guideline S Reference Number	tudy Name		RID amber	Submitter Statu	Note Report Number	-	Description

		42055304	264	PER	BR 1761 (TGAI)	
63-17	Storage stability	42256302	264	PER	BR 1766 (Formulation)	
63-18	Viscosity		264	PER		N.A Solid
63-19	Miscibility		264	PER		N.A Solid
	-	42055304	264	PER	BR 1761 (TGAI)	
63-20	Corrosion characteristics	42256302	264	PER	BR 1766 (Formulation)	
63-21	Dielectric breakdown volt					N.A Solid
64-t	Submittal of samples				Samples available upon request	
830-Group A	Product Chemistry: Identity, Composition, Analysis	45096902	11556	OWN	Report No. 75133	Submitted with application for Advantage Plus 9 for Cats
830-Group B	Product Chemistry: Physical/Chemical Properties	45096903	11556	OWN	Report No. 75132	Submitted with application for Advantage Plus 9 for Cats
Wildlife and Aqu	atic Organisms, Section 158.490					
71-1	Acute avian oral - quail/duek					N.A.
71-2(a)	Avian dietary - quail					N.A.
71-2(b)	Avian dietary - duck					N.A.
71-3	Wild mammal toxicity					N.A.
71-4(a)	Avian reproduction - quail					N.A.
71-4(6)	Avian reproduction - duck					N.A.
71-5	Simulated or actual field study					N.A.
72-1(a)	Fish toxicity - bluegill			· ·		N.A.
72-1(b)	Fish toxicity bluegill - tep	<u> </u>				N.A.
72-2(a)	Invertebrate toxicity - Daphnia			1		N.A.



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			DATA	MATRIX		
Date: September 1	14, 2007		EPA Reg No	/FileSymb	or: 11556-REt, 11556-REL 11556-RET, 11556-RGN	Page 4 of 11
Bayer Health Care LLC Animal Health Division P.O. Box 390 Shawnee Mission, KS: 66201-0390			A	dvantage® I dvaotage® I	Pus 10 for Dogs Pus 20 for Dogs Pus 55 for Dogs Pus 100 for Dogs	Ingredient: imidacloprid, CAS = 138261-41-3 Pyriproxyfen, CAS = 95737-68-1
Guideline Reference Number	Gutdeline Study Name.	MRID Number	Submitter	Status	Note Report Number	Description
72-2(b)	Invertebrate toxicity - Amphipods			<u> </u>		N.A.
72-2(c)	Acute aquatic invertebrate toxicity - Chironomids					N.A
72-3(a)	Estuarine / manine toxicity - fish		l			N.A.
72-3(b)	Estuarine / marine toxicity - mollusk					N.A.
72-3(c)	Estuarine/marine toxicity - shrimp					N.A.
72-4(a)	Early life stage - fish					N.A.
72-4(b)	Life cycle invertebrate			İ		N.A.
72-7	Simulated or actual field study	J		,		N.A.
None	Foliar hatf-life and distribution for potatoes			[N.A.
None	Runoff and Erosion predictions for apple/potato/cotton					N.A.
None	Risk assessment for apple/potato/cotton					N.A.
None	PELMO Modeling - sugarbeet/Germany	:				N.A.
Toxicology, Section	on 158.340					
		42055331	264	PER	Report No. 100040 (TGAI)	-
		42256313	264	PER	Report No. 100010 (2 F)	
	· ·	4342820t	264	PER	Report No. 106380 (1.6 F)	
		43679601	11556	OWN	Report No. 74585 (Adv)	
		45096904	11556	OWN	Report No. 75195 (Adv Plus)	Submitted with application for Advantage Plus 9 for Cats
81-1	Acute oral toxicity rat	47089411	11556	OWN	Report No. 75922 (Adv Plus)	Submitted with application for Advantage Plus 9 for Cats



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	DATA MATRIX	
Date: September 14, 2007	EPA Regino, File Symbol: 11556-REI, 11556-REL 11556-RET, 11556-RGN	Page 5 of II
Bayer HealthCare LLC Animal Health Division P.O. Box 390 Shawnee Mission, KS 66201-0390	Product: Advantage® Plus 10 for Dogs Advantage® Plus 20 for Dogs Advantage® Plus 55 for Dogs Advantage® Plus 100 for Dogs	Ingredient: Imidacloprid, CAS = 138261-41-3 Pyriproxyfen, CAS = 95737-68-1
Guideline Guideline Study Name MRID Reference Number	Submitter Status Report Number	Description

,		42055332	264	PER	Report No. 100041 (TGAI)	
		42256315	264	PER	Report No. 100002 (2 F)	
		43428201	264	PER	Report No. 106380 (1.6 F)	
	İ	4379602	11556	OWN	Report No. 74584 (Adv)	
81-2	Acute dermal toxicity, rat/rabbit	45096905	11556	OWN	Report No. 75196	Submitted with application for Advantage Plus 9 for Cats
		42055333	264	PER	Report No. 99806 (TGAI)	
	1	42286101	264	PER	Report No. 99806-1 (TGAI)	
		42256317	264	PER	Report No. 100012 (2 F)	
		43428201	264	PER	Report No. 106380 (1.6 F)	
	i	43679603	11556	OWN	Report No. 74589 (Adv)	
81-3	Acute inhalation toxicity, rat	45096906	11556	OWN	Report No. 75197 (Adv Plus)	Submitted with application for Advantage Plus 9 for Cals
		42055334	264	PER	Report No. 99679 (TGAI)	
		42256319	264	PER	Report No. 99815 (2 F)	
	ļ	43428201	264	PER	Report No. 106380 (1.6 F)	
		43428201	264	PER	Report No. 106380 (1.6 F)	
		43679604	11556	OWN	Report No. 74588 (Adv)	
81-4	Primary eye irritation - rabbit	45096907	11556	OWN	Report No. 75199 (Adv Plus)	Submitted with application for Advantage Plus 9 for Cats



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	DATA MATRIX	
Date: Sepleinber 14, 2007	EPA Reg No./FileSymbol: 11556-REL, 11556-REL 11556-RET, 11556-RGN	Page 6 of 11
Bayer Health Care LLC Antimal Health Division P.O. Box 390 Shawner Mission, KS 66201.0390	Product: Advantage® Plus 10 for Dogs Advantage® Plus 20 for Dogs Advantage® Plus 55 for Dogs Advantage® Plus 100 for Dogs	Ingredient: Imidacloprid, CAS = 13826t-41-3 Pyriproxyten, CAS = 95737-68-1
Guideline Guideline Study Name MRID Reference Number	Submifter Status Note Report Number	Description

		42055335	264	PER	Report No. 99804 (TGAI)	
		42256321	264	PER	Report No. 99816 (2 F)	-
	<u> </u>	43428201	264	PER	Report No. 106380 (1.6 F)	·
		43679605	11556	OWN	Report No. 74586 (Adv)	
81-5	Primary dermal irritation - rabbit	45096908	11556	OWN	Report No. 75200 (Adv Plus)	Submitted with application for Advantage Plus 9 for Cats
		42055336	264	PER	Report No. 99800 (TGAI)	
	Ì	42256323	264	PER	Report No. 100003 (2 F)	
		43428201	264	PER	Report No. 106380 (1.6 F)	
		43679606	11556	OWN	Report No. 74587 (Adv)	
81-6	Dermal sensitization - guinea pig	45096909	11556	OWN	Report No. 75201 (Adv Plus)	Submitted with application for Advantage Plus 9 for Cats
		43170301	264	PER	Report No. 106348	
81-8[55)	Acute neurotoxicity	43285801	264	PER	Report No. 106348-1	
82-l(a)	90-day feeding - rodent	42256327	264	PER	Report No. 100036	
82-1(b)	90-day feeding - non-rodent	42256328	264	PER	Report No. 100176	
82-2	21-day dermal - rabbit/rat	42256329	264	PER	Report No. 100688	
82-5(b)	90 day neurotoxicity - mammal	43286401	264	PER	Report No. 106356	
		42256331	264	PER	Report No. 100652	
		42256332	264	PER	Report No. 101931	
		42256333	264	PER	Report No. 102658	
83-l(a)	Chronic feeding toxicity - rodent	42256334	264	PER	Report No. 99672	
83-1(b)	Chronic feeding toxicity - non-rodent	42273002	264	PER	Report No. 100015	



			DATA	MATRIX		· · · · · · · · · · · · · · · · · · ·
Date: September 14	1, 2007		EPA Reg No	o/FileSymbo	l: 11556 REI, 11556 REL 11556 RET, 11556 RGN	Page 7 of 11
Date: September 14, 2007 Bayer Health Care LLC Animal Health Division P.O. Box 390 Shawnee Mission, KS 66201-0390			A	.dvanlage® Pl .dvantage® Pl	us 10 for Dogs us 20 for Dogs us 55 for Dogs us 100 for Dogs	Ingredient: Imidacloprid, CAS = 138261-41-3 Pyriproxyfon, CAS = 95737-68-1
Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	1	Note Report Number	Description
		42256331	264	PER	Report No. 100652	
		42256332	264	PER	Report No. 101931	
		42256333	264	PER	Report No. 102658	
83-2(a)	Oncogenicity - rat	42256334	264	PER	Report No. 99672	
		42256335	264	PER	Report No. 100693	
		42256336	264	PER	Report No. 101929	
83-2(b)	Oncogenicity - mouse	42256337	264	PER	Report No. 99808	
83-3(a)	Developmental toxicity - rat	42256338	264	PER	Report No. 98571	
83-3(b)	Developmental toxicity - rabbit	42256339	264	PER	Report No. 98572	
83-4	Two generation reproduction - rat	42256340	264	PER	Report No. 100647	
		42256341	264	PER	Report No. 101276	-
		42256342	264	PER	Report No. 98584	
84-2(a)	Gene mutation (ames test)	42256343	264	PER	Report No. 98570	
		42256344	264	PER	Report No. 100021	
	,	42256345	264	PER	Report No. 99262	
		42256346	264	PER	Report No. 99257	
		42256347	264	PER	Report No. 102652	
04.24.3	Structural chromosomal aberration	42256348	264	PER	Report No. 102654	
84-2(b)		42256349	264	PER	Report No. 102655	
		42256350	264	PER	Report No. 99676	
		42256351	264	PER	Report No. 101275	
54.4		42256352	264	PER	Report No. 98573	
84-4	Other genotoxic effects	42256353	264	PER	Report No. 102653	



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-3_11	a the territoria dia discrete	*	DATA	MATRIX		
Date: September 1	4, 2007		EPA Reg No		ol: 11556-REI, 11556-REL 11556-RET, 11556-RGN	Page 8 of 11
Bayer Health Care I Animal Health Divi P.O. Box 390 Shawnee Mission, I		A	.dvantage® P .dvantage® P	lus 10 for Dogs lus 20 for Dogs lus 55 for Dogs lus 100 for Dogs	Ingredient: Imidacloptid. CAS = 138261-41-3 Pyriproxyfen, CAS = 95737-68-1	
Guideline Reference Number	Guideline Study Name	MRID Number	Submitter	Status	Note Report Number	Description
	<u> </u>	42256354	264	PER	Report No. 101999	1
		42256355	264	PER	Report No. 87264	-
	1	42256356	264	PER	Report No. 87265	
85-1	General metabolism	42256357	264	PER	Report No. 102617	
		43679607	11556	OWN	Report No. 74580 (Adv)	Dogs
		43679608	11556	OWN	Report No. 74590 (Adv)	Dogs
870.7200		44099801	11556	OWN	Report No. 74730 (Adv)	Puppies
		45097102	11556	OWN	Report No. 75121 (Adv Plus)	Dogs
(86-1)	Domestic Animal Safety	45097101	11556	OWN	Report No. 75119 (Adv Plus)	Puppies
		43679503	11556	OWN	Report No. 74571 (Adv)	Cats
		43679504	11556	OWN	Report No. 74581 (Adv)	Cats
		43679609	11556	OWN	Report No. 74572 (Adv)	Dogs
		43679610	11556	OWN	Report No. 74541 (Adv)	Dogs
_		44256901	11556	OWN	Report No. 74800 (Adv)	Speed of flea kill
		44256902	11556	OWN	Report No. 47828 (Adv)	Larvicidal efficacy
		44256903	11556	OWN	Report No. 74792 (Adv)	Effects of shampooing
		47109101	11556	OWN	Report No. 75867 (K9)	Waterproof
		45086801	1021	PER	Report No. OT018-94	Pyriproxyfon efficaey
		45086801	1021	PER	Report No. OT016-93	Pyriproxyfen efficacy
		45086801	1021	PER	Report No. OT006-96	Pyriproxyfen efficacy
95-9	Efficacy	47190401	11556	OWN	Report No. 75950 (Advantage)	Lice
Plant Protection, 1 158.540	Section	12				
122-2	Aquatic plant growth		Ι΄ ΄	T		N.A.
123-2	Aquatic plant growth	ļ	1	1		N.A.



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		DATA MATRIX		
Date: September 14, 2007			6-rei, 11556-rel 6-ret, 11556-rgn	Page 9 of 11
Bayer Health Care LTC Animal Health Division P.O. Box 390 Shawnœ Mission, KS 66201-0390		Product: Advantage® Plus 10 for Do Advantage® Plus 20 for Do Advantage® Plus 55 for Do Advantage® Plus 100 for D	egs egs	Ingredient: Imidæclopnd, CAS = 138261-41-3 Pyriproxyfen, CAS = 95737-68-1
Guideline Guideline Study Name Reference Number	MRID Number	Submitter Status Note Report N	umber	Description

Non-Target Inse Section 158.590	ects,		nte · ·		
141-1	Honey bee acute contact	1			N.A.
141-2	Honey bee residue on foliage				N.A.
Recutry Protecti Section 158,390	on,				
230-236	Mixer/loader/applicator exposure				N. A.
Environmental J Section 158,290					
161-1	Hydrolysis				N.A.
161-2	Photodegradation - water				N.A.
t6t-3	Photodegradation - soil				N.A.
t 62-1	Aerobic soit metabotism				N.A.
162-2	Anerobic soil metabolism				N.A.
162-3	Anaerobic aquatic metabolism				N.A.
163-1	Leaching / adsorption/desorption				N.A.
164-1	Terrestrial field dissipation				N.A.
165-1	Confined rotational crop				N.A.
165-2	Field rotational crop			<u> </u>	N.A.
166-1	Ground water - small prospective				N.A.
None	Environmental fate summary				N.A.



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		 	DATA MATRIX		
Date: September 14, 2007			EPA Reg No./File Symbo	i: 11556-rel 11556-rel 11556-ret, 11556-rgn	. Page 10 of 11
Bayer HealthCare LLC Animal Health Division P.O. Box 390 Shawnee Mission, KS 6620	1-0390				Ingredient: Imidaeloptid, CAS = 138261-41-3 Pyriproxyfen, CAS = 95737-68-1
Guideline Guideli Reference Number	ine Study Name	MRID Number	.Submitter Status	Note Report Number	Description

Residuc, Section	158.240					
171-l(a)	Nature of residue - plants	1		<u> </u>	1	N.A.
171-4(ъ)	Nature of residue - livestock and poultry	· · · · · · · · · · · · · · · · · · ·			1	N.A.
171-4(c)	Residue analytical method - plants					N.A.
171-4(d)	Residue analytical method - animal	 				N.A.
171-4(e)	Storage stability				T	N.A.
171-4(j)	Magnitude of residues - meat/milk/poultry/egg	<u> </u>				N.A.
171-4(k)	Magnitude of residue - crop field trials			ļ	1	N.A.
171-4(1)	Magnitude of residue - processed food/feed					N.A.
171-4(m)	Method validation/ multiresidue method	<u> </u>			T	N.A.
None	Benefits Reports		·		<u> </u>	
None	Dietary Analysis					N.A.
Child-Reesistan	t Packaging, Section 157			j	T	
157.20	Standards - Child-Resistant Packaging Testing	47089407	11556	OWN	Report No. 75913	Submitted with Advantage Plus 9 for Cats; 0.4 mL/4pl/Child
		47089408	11556	OWN	Report No. 75914	Submitted with Advantage Plus 9 for Cats; 0.4 mL/4pk/Adult
		47089409	11556	OWN	Report No. 75915	Submitted with Advantage Plus 9 for Cats; 0.4 mL/6pl/Child
		47089410	11556	OWN	Report No. 75916	Submitted with Advantage Plus 9 for Cats; 0.4 mL/6pk/Aduh
		47089103	11556	OWN	Report No. 75897	Submitted with Advantage Plus 20 for Dogs; 1.0 mL/4pk/Child



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		1 - 1 - 1 - 1 - 1 - 1 - 1 - 1 - 1 - 1 -		DATA	MATRIX		·	·
Date: September 14,				EPA-Reg No.	/File Symb	of: 11556-REL, 11556-REL 11556-RET, 11556-RGN	Page 11 of 11	
Bayer HealthCard LI Animal Health Divis P.O. Box 390 Shawnee Mission, K	ion			Ac Ac	oduct: Advantage® Plus 10 for Dogs Advantage® Plus 20 for Dogs Advantage® Plus 55 for Dogs Advantage® Plus 100 for Dogs			loprid, CAS = 138261-41-3- exyfen, CAS = 95737-68-1
		- : : : : : : : : : : : : : : : : : : :				Note		
Guideline Reference Number	Guideline Study Name		MR1D Number	Submitter		Report Number	Description	
	**************************************		47089104	11556	OWN	Report No. 75898	Submitted with Ad 1.0 mL/4pk/Adult	vantage Plus 20 for Dogs;
			47089101	11556	OWN	Report No. 75893	Submitted with Ad 1.0 mL/6pk/Child	vantage Plus 20 for Dogs;
			47089102	11556	OWN	Report No. 75894	Submitted with Ad 1.0 mL/6pk/Adult	vantage Plus 20 for Cats;
			47089201	11556	OWN	Report No. 75905	Submitted with Ad 2.5 mL/4PK/Child	vantage Plus 55 for Dogs;
			47089202	11556	OWN	Report No. 75906	Submitted with Ad 2.5 mL/4PK/Adult	vantage Plus 55 for Dogs;
			47089203	11556	OWN	Report No. 75907	Submitted with Ad 2,5 mL/6PK/Child	vantage Plus 55 for Dogs;
			47089204	11556	OWN	Report No. 75908	Submitted with Ad 2.5 mL/6PK/Adult	vantage Plus 55 for Dogs;
			47089301	t1556	OWN	Report No. 75909	Submitted with Ad 4.0 mL/4PK/Child	vantage Plus 100 for Dogs;
]	•		47089302	11556	OWN	Report No. 75910	Submitted with Ad 4.0 mL/4PK/Adult	vantage Plus 100 for Dogs;
ļ			47089303	11556	OWN	Report No. 75911	Submitted with Ad 4.0 mL/6PK/Child	vantage Plus 100 for Dogs;
	\cap		47089304	11556	OWN	Report No. 75912	Submitted with Ad 4.0 mL/6PK/Adult	vantage Plus 100 for Dogs;
Signature 1	Cafho A.	Spile				nglas A. Spilker nager, EPA Regulatory Affairs		September 14, 2007



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			DATA	MATRIX		
Date: August 15,	2007		EPA Reg No	o./File Symb	ol: 11556-132, 11556-135 11556-133, 11556-134	Page 1 of 10
Bayer Health Care, LLC Animal Health Division P.O. Box 390 Shawnce Mission, KS 66201-0390			K K	(9 Advantix@ (9 Advantix@	0 10 for Dogs 0 20 for Dogs 0 55 for Dogs 0 100 for Dogs	Ingredient: Imidacloprid, CAS = 138261-41-3 Permethrin, CAS = 52645-53-1
Guideline Reférence Number	Guideline Study Name	MRID Number	Submitter	Status	Note Report Number	Description
	177					
	-	*** 3.7	3125	PER		
		-,	3125	PER		
			3125	PER		
	1 1 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2		3125	PER		
		7-	3125	PER		
			3125	PER		
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				DATA	MATRIX		
Date: August 15,		EPA Reg No	/File Symb	ol: 11556-132, 11556-135 11556-133, 11556-134	Page 2 of 10		
Bayer Health Care, LLC Animal Health Division P.O. Box 390 Shawnee Mission, KS 66201-0390			ļ ĸ	9 Advantix® 9 Advantix®	0 10 for Dogs 0 20 for Dogs 0 55 for Dogs 0 100 for Dogs	Ingredient: Imidacloprid, CAS = 138261-41-3 Permethrin, CAS = \$2645-53-1	
Guideline	C the Control					Nole	
Reference Number	Guideline Study Name		MRID Number	Submitter	Status	Report Number	Description
7 17.	<u> </u>			3125	PER		
			: · · · · · · · · · · · · · · · · · · ·	3125	PER	[
		37.15	·	3125	PER		
	<u>} ·</u>			3125	PER		
	(3125	PER		
N. 1	<u> </u>		24,	3125	PER		
-		7 47 12 47 12 12 12 12 12 12 12 12 12 12 12 12 12		3125	PER		
· - 				3125	PER		
	<u> </u>			3125	PER	<u> </u>	
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Date: August 15	, 2007		EPA Reg No	./File Symb	ol: 11556-132, 11556-135 11556-133, 11556-134	Page 3 of 10
Bayer Health Care, LLC Animal Health Division P.O. Box 390 Shawnee Mission, KS 66201-0390			Product: K9 Advantix® 10 for Dogs K9 Advantix® 20 for Dogs K9 Advantix® 55 for Dogs K9 Advantix® 100 for Dogs			logredicot: Imidaeloprid, CAS = 138261-41-3 Permethrin, CAS = 52645-53-1
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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

~	end the form to the address.		DATA	MATRIX		
Date: August 15	5, 2007		EPA Reg No	/File Symb	bl: 11556-132, 11556-135 11556-133, 11556-134	Page 10 of 10
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Bayer CropScience



February 28, 2007

Document Processing Desk Office of Pesticide Programs (7505P) U.S. Environmental Protection Agency Room S-4900, One Potomac Yard 2777 South Crystal Drive Arlington, Virginia 22202-4501

Attention: Mr. Tom Harris (PM 01, RD)

Re: Letter of Authorization: Imidacloprid

Bayer HealthCare LLC, Animal Health Division (BHC) -

Advantage® Plus Application for Registration

Dear Mr. Harris,

Bayer CropScience LP (BCS) hereby authorizes the Agency to refer to any research and/or test data on our active ingredient imidacloprid (the active ingredient in ADMIRE® and PROVADO®) in support of the applications for registration of Advantage® Plus 9 (EPA File Symbol: 11556-REA), Advantage® Plus 18 (EPA File Symbol: 11556-REO), Advantage® Plus 10 (EPA File Symbol: 11556-REI), Advantage® Plus 20 (EPA File Symbol: 11556-RET) and Advantage® Plus 100 (EPA File Symbol: 11556-RGN), submitted by Bayer HealthCare LLC, Animal Health Division (BHC), P.O. Box 390, Shawnee Mission, KS, 66201-0390.

Furthermore, BCS and BHC are wholly owned subsidiaries of Bayer Corporation. Both companies seek product registrations for products containing the active ingredient imidacloprid. Any confidential business information released by the Agency in data evaluation records or other documents for company number 264 can be disclosed without restriction to the BHC, company number 11556. In addition, the Agency is authorized to refer to any research and/or test data submitted under company number 264 in support of applications for registration from Bayer HealthCare LLC, Animal Health Division (BHC), company number 11556.

Bayer Crop**S**cience 2 T.W. Alexander Drive P. O. Box 12014 Research Triangle Park NC 27709 Tel: 919 549-2000

297

Please contact me at <u>jamin.huang@bayercropscience.com</u> or at 919-549-2634 if you have any questions regarding this submission.

Sincerely,

Jamin Huang, Ph.D.

Product Registration Manager

CC: Doug Spilker, Ph.D., Bayer HealthCare LLC, Animal Health Division



McLAUGHLIN GORMLEY KING COMPANY

8810 Tenth Avenue North • Minneapolis, MN 55427-4319 U.S.A. 763-544-0341 • 800-645-6466 • Fax 763-544-6437 • www.mgk.com February 28, 2007

Mr. Tom Harris, Acting PM 1
Office of Pesticide Programs (H7504P)
U.S. Environmental Protection Agency
Room S-4900, One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202-4501

Subject:

Bayer Animal Health

Dear Mr. Harris:

This letter serves as authorization, in accordance with our agreement with the registrant, to refer to the following data submitted by McLaughlin Gormley King Company to EPA for the subject company's registration.

MGK Efficacy Data:

MRID #45086801 - Submitted to EPA Reg. No. 1021-1619

Registrant's Product: Advantage® Plus 9

Advantage® Plus 18 Advantage® Plus 10 Advantage® Plus 20 Advantage® Plus 55 Advantage® Plus 100

EPA Reg. Nos.:

11556-REA 11556-REO 11556-REI 11556-REL 11556-RET 11556-RGN

Although this is authorization to rely on MGK data for the subject company's subject registration, absolutely no data of a confidential nature is to be disclosed to them.

Sincerely,

McLAUGHLIN GORMLEY KING COMPANY

July & Schletan

Julie B. Schlekau

Registration Specialist

Fee for Service

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This package includes the following

- New Registration
- Amendment

Studies? Fee Waiver?

volpay % Reduction: ½ %

for Division

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· RD

Risk Mgr.

Receipt No.

EPA File Symbol/Reg. No.

Pin-Punch Date:

S-807420

11556-REI

3/9/2007

Fee for Service



This package includes the following	for Division
New Registration Amendment Studies? Fee Waiver? Volpay % Reduction: 10/2	○ AD ○ BPPD ○ RD Risk Mgr. ②
Receipt No. S-EPA File Symbol/Reg. No. Pin-Punch Date: This item is NOT subject to	11576-RIEL 10-21531 3/8/27
Action Code: Requested: Granted: Amount Due: \$ 945.00	Parent/Child Decisions:
Reviewer:	Date: 7/23/07



UNITÉ. STATES ENVIRONMENTAL PROTECTION AGENCY WASHINGTON, D.C. 20460

March 23, 2007

OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

PLEASE RETURN A COPY OF THIS LETTER WITH PAYMENT

OPP Decision Number: D-215323

EPA File Symbol or Registration Number: 11556-REI

Product Name: Advantage Plus 10 for Dogs

EPA Receipt Date: 09-Mar-2007 EPA Company Number: 11556

Company Name: BAYER HEALTHCARE LLC

TERRY MCNAMARA
BAYER HEALTHCARE LLC
ANIMAL HEALTH DIVISION
PO Box 390
SHAWNEE MISSION, KS 66201-0390

SUBJECT: Receipt of Registration Service Fee Voluntary Payment Notice

Dear Registrant:

The Office of Pesticide Programs has received your Notice of Intent to Submit Voluntary Payment for the action described below.

The Action has been identified as Action Code: R31.1

NEW PRODUCT; NON-FAST TRACK (INCLUDES REVIEWS OF PRODUCT CHEMISTRY; ACUTE TOXICITY; PUBLIC HEALTH PEST EFFICACY); Reduced Fee: Linked to PRIA Application;

The net amount due was calculated by determining the fee associated with this action (from the March 17, 2004 Federal Register Notice). Any previously submitted tolerance fees were subtracted from this amount. This amount was further reduced in proportion to the amount of work that has been done on the action prior to March 23, 2004.

You may be eligible for a i... or partial waiver of the registration service if, for example, you qualify as a small business or are applying for a minor use, or if your application is solely associated with an IR-4 tolerance petition. Please be advised that if you intend to request a waiver, you must do so in writing within 15 days of receipt of this invoice instead of remitting the amount indicated below. OPP will not consider waiver requests after the registration service fee has been paid. Information regarding eligibility and how to request and document a fee waiver is available on the OPP Fee for Service web site at www.epa.gov/pesticides/fees.

Please remit payment in the amount of: \$ 945 to:

By USPS:

USEPA Washington Finance Center Pesticide Registration Service Fee PO Box 360277 Pittsburgh, PA 15251

By Courier:

U.S. EPA Washington Finance Center Pesticide Registration Service Fee C/O Mellon Client Service Center 500 Ross Street, Room 670 Box 360277 Pittsburgh, PA 15251-6277 Attn: EPA Module Supervisor

Telephone: (412) 236-2294

All payments must be in United States currency by check, bank draft, or money order drawn to the order of the Environmental Protection Agency. To ensure proper credit, please write the OPP DECISION NUMBER on your check, and enclose a copy of this letter with your payment.

If the Agency does not receive certification of payment of this voluntary fee within the next 90 days, the Agency will presume that you no longer want this action to be considered under the Pesticide Registration Improvement Act (PRIA). The Agency would then return this action to its place in the registration queue with other pending actions not subject to the decision time review period requirements of PRIA.

If you have any questions, please contact the Pesticide Registration Service Fee Ombudsman at (703) 305-6249.

Registration Division